Kidney Medicine

Serum Bicarbonate and Graft and Patient Outcomes Among Kidney Transplant Recipients: A Retrospective Cohort Study Evaluating Changes in Serum Bicarbonate Over Time

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Rationale & Objective: Identification of treatable risk factors for kidney allograft failure is necessary to improve graft longevity. Metabolic acidosis with either low serum bicarbonate or normal serum bicarbonate (eubicarbonatemic metabolic acidosis) is implicated in native kidney disease progression but its effects in kidney transplant recipients are unclear.

Study Design: Retrospective cohort study.

Setting & Participants: An Integrated Claims-Clinical dataset of US patients with chronic kidney disease (estimated glomerular filtration rates <60 mL/min/1.73 m^2) and serum bicarbonate data were used to generate a cohort of kidney transplant recipients with data from ≥1 year before and after transplantation.

Primary Predictor: The primary independent variable was a change in serum bicarbonate from baseline.

Outcomes: The primary outcomes were graft failure and all-cause mortality. The secondary outcomes were major adverse cardiac events and all-cause hospitalization.

Analytical Approach: We used adjusted time-dependent Cox proportional hazards models to assess the risk of graft failure, all-cause mortality, major adverse cardiac events, and time to first hospitalization.

Results: In this US community-based cohort of 1,915 kidney transplant recipients with a median follow-up of ∼2.5 years, each 1-mEq/L increase in serum bicarbonate was associated with significantly lower hazard of graft loss, death, major adverse cardiac events, and hospitalization by 10%, 8%, 4%, and 8%, respectively.

Limitations: Possible residual confounding.

Conclusions: In a US community-based population of kidney transplant recipients, even small incremental increases in serum bicarbonate (1 mEq/L) were significantly associated with reduced hazard of graft loss, all-cause mortality, cardiovascular events, and hospitalization. Interventional trials evaluating the potential benefits of treating metabolic acidosis in kidney transplant recipients are warranted.

Visual Abstract included

Complete author and article information provided before references.

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In the United States, graft survival rates at 1-year and 5-years posttransplant decline from 93.4% to 72.4% and from 97.2% to 84.6% in deceased and living donor transplants, respectively.[1] At 10-years posttransplant, approximately 50% of deceased donor transplants and 30% of living donor allografts are no longer functional either due to graft loss or to death with a functioning graft.[2]

The pathogenesis of graft failure is multifactorial and includes both immunologic and nonimmunologic factors and is often preceded by progressive loss of graft function.[2-4] Indeed, the prevalence of interstitial fibrosis and tubular atrophy is as high as 60%-70% on protocol biopsies after the first year.[3] Identification of treatable risk factors for progressive loss of graft function is necessary to improve graft longevity, reduce the need for retransplantation, and to optimize patient outcomes.

Metabolic acidosis is a process that results in net acid retention. It is not defined by any particular level of serum bicarbonate. Renal ammoniagenesis, and consequently, the ability to excrete acid decline progressively with loss of kidney function.[5] This impairment results in demonstrable acid retention even in patients with earlier stages of chronic kidney disease (CKD) (ie, stage 2, estimated glomerular filtration rates [eGFRs] 60-89 mL/min/1.73 m^2) whose serum bicarbonate levels are normal, a phenomenon known as eubicarbonatemic metabolic acidosis.[6,7] Acid retention results in adaptations such as release of bone alkali, renal tubular hypertrophy, and muscle catabolism that are ultimately maladaptive, contributing to bone demineralization, renal fibrosis, and loss of muscle mass.[5] Thus, a decrease in serum bicarbonate below the normal range is a late finding in the course of chronic metabolic acidosis in patients with CKD.[8]

Metabolic acidosis with low serum bicarbonate (<22 mEq/L) is an independent risk factor for CKD progression and may also be a salient factor in the loss of graft function in transplanted kidneys.[9] Bicarbonate levels within the lower end of the normal range may also be associated with higher risk. A previous study in a Korean cohort of kidney transplant recipients (KTRs) showed that metabolic acidosis 3 months after kidney transplantation was associated with an increased risk of graft loss, with risk of graft loss that reached a nadir at serum bicarbonate levels between 26-28 mEq/L.[10]

However, such an analysis has not been reported from a large US KTR population. Here we report the association of changes in serum bicarbonate on graft loss, mortality,

PLAIN-LANGUAGE SUMMARY

Kidney transplantation is a life-saving procedure that allows patients with kidney failure to live without dialysis treatments. However, kidney transplants often fail during the lifetime of the recipient, requiring them to return to dialysis. We need to identify treatable factors that contribute to kidney transplant failure. We examined the role of changing serum bicarbonate, a measure of the body's acid-base balance, in kidney transplant loss. We found that rising serum bicarbonate (suggesting a less acidic body environment) was associated with a significantly reduced chance of kidney transplant loss, death, major heart problems, and hospitalization. These findings are important because they may lead to studies to determine if treatments aimed at increasing serum bicarbonate benefit longevity of kidney transplants.

cardiovascular outcomes, and hospitalizations from a diverse community-based cohort of over 1,900 KTRs from the United States.

METHODS

Study Design and Data Sources

In this retrospective cohort study, we analyzed data from Optum's deidentified Integrated Claims-Clinical dataset of US patients (2007-2019) with advanced CKD and serum bicarbonate data (≥ 3 eGFR results <60 mL/min/1.73 m^2 and ≥ 3 serum bicarbonate results with at least 1 result between 12 and 29 mEq/L) (Fig 1). Data collection for the data extract included records from January 2007 through June 2019. We selected patients for this study from this data extract. Study cohort patients were required to have a kidney transplant procedure (by procedure code or Diagnosis-Related Group) during an inpatient admission, preceded by ≥ 1 year of data that included at least one serum bicarbonate value between 12 and 40 mEq/L. Inclusion further required patient survival and electronic health records (EHR) data for ≥ 1-year posttransplant, and ≥ 1 value each for eGFR and serum bicarbonate in the period 6-12 months after transplantation. Patients were excluded if there was evidence that another major organ other than the pancreas was transplanted before or concurrent with the kidney transplantation.

The Optum dataset is a longitudinal clinical repository which contains over 103 million people with all types of health insurance plans, including those who are uninsured, from all 50 states in the United States and Puerto Rico. Extracted data elements utilized for this analysis were derived from inpatient and outpatient EHRs and administrative systems, including laboratory results, coded diagnoses and procedures, and provider notes extracted by natural language processing. Informed consent and institutional review board oversight were not required because the dataset included only deidentified information. Specific definitions, sources, data period activity, and data cleaning methods are summarized in Table S1.

Variables

Baseline characteristics and covariates were consistent with prior research[11] and were defined during 4 time points and intervals: (1) at transplant; (2) during the first full year posttransplant; (3) during the baseline period starting 6 months posttransplant; and (4) during the outcome period starting 12 months posttransplant (Fig 2). Patient demographics, comorbid conditions, prior kidney transplant status, donor type, and induction immunosuppression were assessed as of the transplant date. Posttransplant infections, new onset diabetes, and use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and diuretics were evaluated for a full year posttransplant, starting 6 months posttransplant for the pharmaceuticals. Other baseline variables, mean and maximum eGFR, blood pressure, and maintenance immunosuppression were defined during the baseline period 6 to 12 months posttransplant. Patients were classified by CKD stage using the mean baseline eGFR. We chose the period 6-12 months posttransplant to define the baseline serum bicarbonate and eGFR because graft function and acid-base balance can be unstable in the earlier posttransplantation period. Specific definitions are summarized in Table S1.

The primary predictor variable was change in serum bicarbonate, which was calculated as the difference from baseline serum bicarbonate value to every serum bicarbonate test during the outcome period until the outcome event, death, or censoring at the end of EHR data. The number of days from index to each subsequent serum bicarbonate test was also retained for use in time-dependent modeling. Multiple test records on a single date were averaged. The secondary predictor variable was mean serum bicarbonate during the baseline period starting 6 months posttransplant.

Outcomes

The primary outcomes were graft failure and all-cause mortality. The secondary outcomes were major adverse cardiac events (MACE+) and all-cause hospitalization.

Outcomes were evaluated during the outcome period starting at 1-year posttransplant (ie, the index date) to the end of available data (Fig 2). Graft failure was defined using diagnosis and procedure codes as earliest occurrence of maintenance dialysis, retransplantation, kidney transplant failure diagnosis, or death. Death was identified by linkage to social security records before data deidentification. MACE+ was identified at the first occurrence during the outcome period of myocardial infarction, stroke, new onset heart failure, a heart failure inpatient admission in a patient with a pretransplant history of heart failure, or

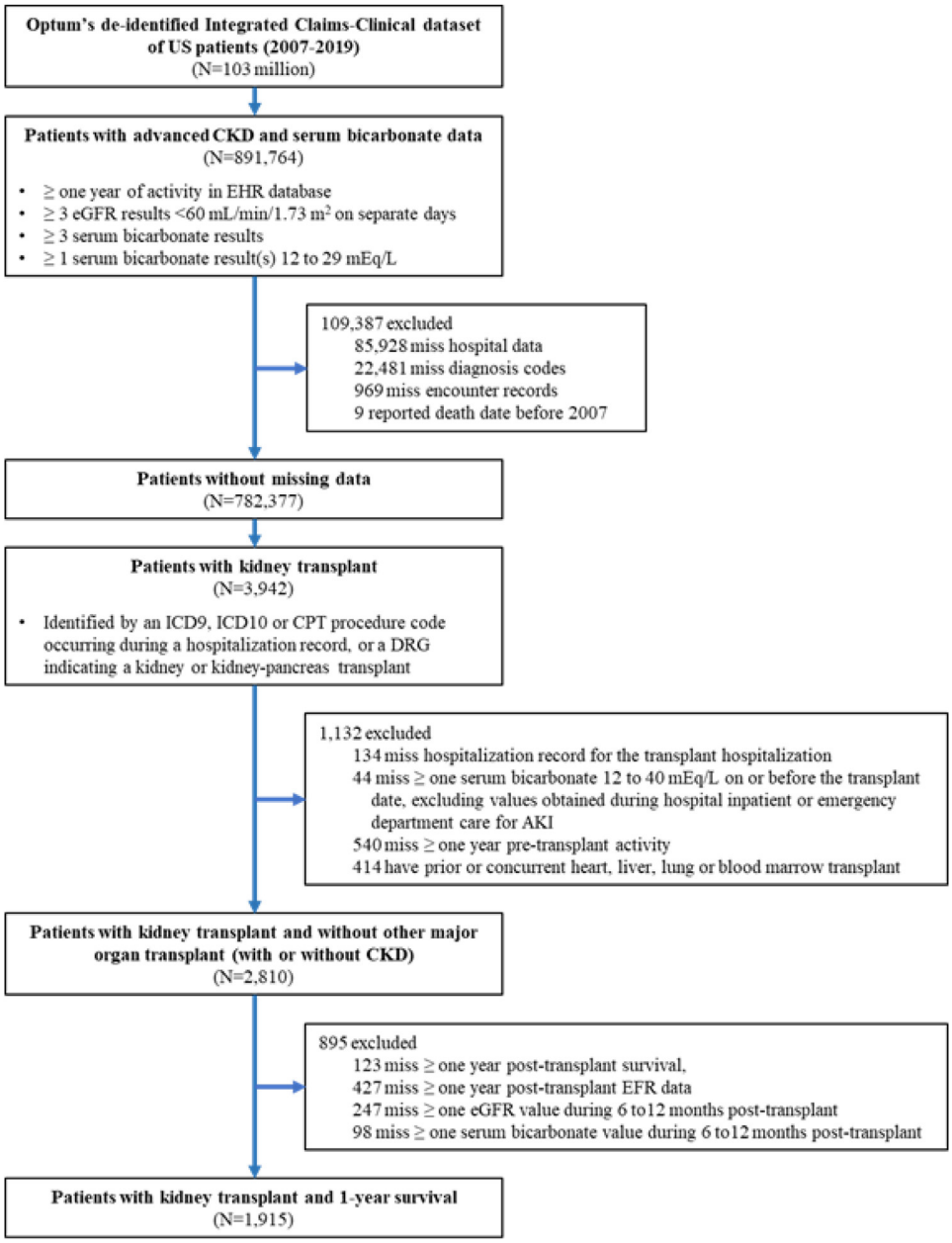

Figure 1. Study cohort selection diagram. Activity in the database was defined by the presence of data point(s) that indicated a likely in-person interaction (eg, measurement of vital signs, collection of laboratory specimens, emergency department discharger) with the patient (see Table S1 for full definition). Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; CPT, current procedural terminology; DRG, diagnosis-related group; eGFR, estimated glomerular filtration rate; EHR, electronic health record; ICD, *International Classification of Diseases*.

cardiovascular death (death within the same or next calendar month as discharge from a hospital inpatient stay with a diagnosis of heart failure, myocardial infarction, or stroke) (Table S1). Hospitalizations were defined as any inpatient hospitalization during the outcome period.

Separate outcome-specific cohorts were established for the graft failure and MACE+ outcomes, in each case excluding patients with evidence of the outcome during the 1 year after transplantation.

Statistical Analysis

Patient characteristics were described using percentage or mean and standard deviation and were reported for each outcome-specific cohort in total and in groups by both baseline serum bicarbonate and change in serum bicarbonate from baseline to the last observation before the event, death, or censoring at end of data. The number and percentage of patients experiencing graft failure, death, or MACE+ were reported for the postindex period. Incidence

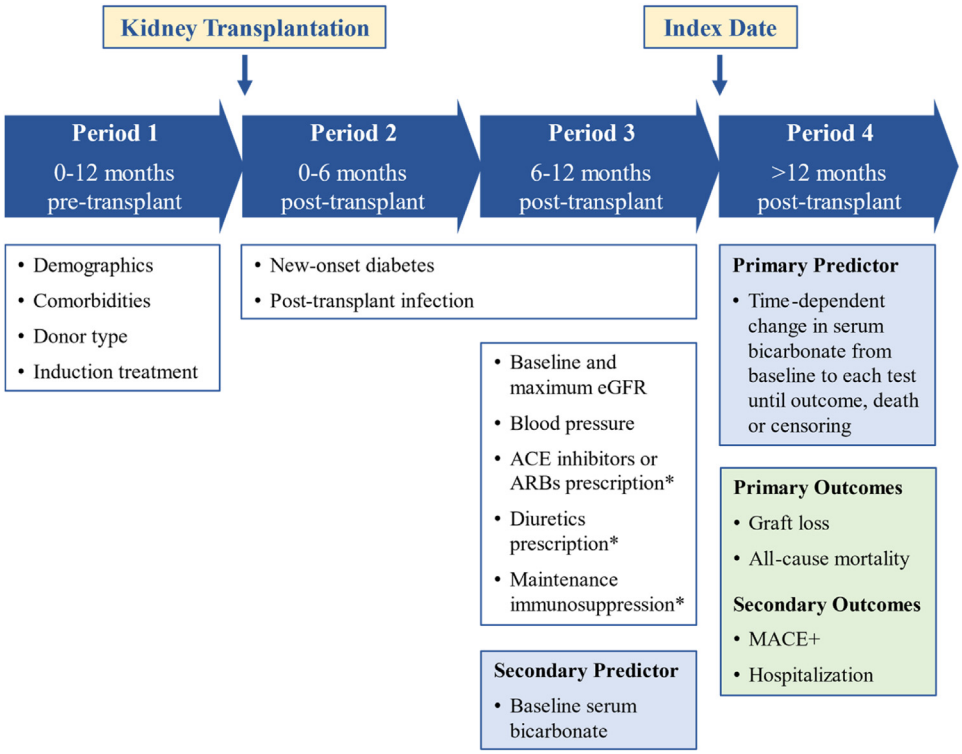

Figure 2. Time periods for assessment of baseline variables, covariates, and outcomes. The primary predictors were baseline serum bicarbonate (assessed 7-12 months posttransplant) and time-dependent change in serum bicarbonate during the outcome period. Outcome variables were graft failure, all-cause mortality, MACE+ (a composite endpoint that included stroke, myocardial infarction, new onset heart failure, heart failure hospitalization in a patient with a pretransplant history of heart failure, and cardiovascular death), and all-cause hospitalization. * Evaluated for 12 months, beginning 6 months posttransplant Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; MACE+, major adverse cardiovascular event.

and frequency of hospitalization were reported for > 1 year and 3 years after the index date.

Because serum bicarbonate is a repeated measures variable where the value for each patient may change, we employed change in serum bicarbonate from baseline in adjusted time-dependent Cox proportional hazards models to assess the hazard of graft failure, all-cause mortality, MACE+, and time to first hospitalization. Data for each patient were presented as multiple observations, and the time interval (number of days postindex) and change in serum bicarbonate value from baseline were evaluated for every postindex test until the outcome event, death, or censoring at the end of EHR data. The time-dependent indicator in our model assessed at each time interval whether a patient had the outcome at that point in time. The hazard at time t was evaluated on the of change in serum bicarbonate at that time, along with the other covariates. A time-dependent Fine and Gray model was used to evaluate a modified graft failure outcome excluding the mortality component, with death as a competing risk. Because a high serum bicarbonate, potentially identifying metabolic alkalosis, has been found to be associated with increased risk of heart failure,[12] we performed sensitivity analyses for all 4 outcomes that excluded patients with serum bicarbonate ≥30 mEq/L at baseline. To assess the possible interaction between baseline serum bicarbonate and change in serum bicarbonate over time, as a further sensitivity analysis we constructed a categorical variable characterizing baseline serum bicarbonate as low (serum bicarbonate 12 to < 22 mEq/L), normal (serum bicarbonate ≥ 22 to < 30 mEq/L), or high (serum bicarbonate ≥ 30 mEq/L) and included an interaction term between the baseline category and the time-dependent change variable for all 4 outcomes. All adjusted statistical models were adjusted for every characteristic listed in Table 1 except for CKD stage. Statistical analyses were performed using SAS/STAT software, version 9.4. *P* values <0.05 were considered statistically significant.

RESULTS

Baseline Characteristics

A total of 1,915 KTRs qualified for the full study cohort. Outcome-specific cohorts varied in size: 1,410 patients in the MACE+ outcome group, which excluded those with a MACE+ event during the first year posttransplant; 1,722 patients in the graft failure group after those with graft

Table 1. Demographics and Clinical Characteristics of the Study Cohort

	Overall Study Cohort (N = 1,915)[a]	Graft Failure Study Cohort (N = 1,722)	MACE+ Study Cohort (N = 1,410)
Characteristics assessed at transplant			
Age (y), mean (SD)	51.2 (16.7)	51.1 (16.7)	49.2 (17.0)
Female, n (%)	758 (40%)	688 (40%)	586 (42%)
Body mass index (kg/m^2), mean (SD)	28.1 (6.1)	28.0 (6.1)	27.8 (6.2)
Race, n (%)			
Asian	128 (7%)	109 (6%)	99 (7%)
Black	477 (25%)	419 (24%)	330 (23%)
Hispanic	265 (14%)	236 (14%)	204 (14%)
Non-Hispanic White	954 (50%)	872 (51%)	704 (50%)
Other/Unknown	91 (5%)	86 (5%)	73 (5%)
Donor type, n (%)			
Living donor	458 (24%)	438 (25%)	350 (25%)
Cadaver donor	1003 (52%)	909 (53%)	726 (51%)
Unknown	454 (24%)	375 (22%)	334 (24%)
Prior transplant	552 (29%)	462 (27%)	400 (28%)
Comorbid conditions, n (%)			
Diabetes	951 (50%)	845 (49%)	646 (46%)
Hypertension	1,777 (93%)	1,595 (93%)	1,302 (92%)
Glomerulonephritis	860 (45%)	768 (45%)	648 (46%)
Cystic kidney disease	381 (20%)	348 (20%)	310 (22%)
Induction immunosuppression, n (%)			
Basiliximab	350 (18%)	327 (19%)	257 (18%)
Anti-thymocyte globulin (rabbit)	971 (51%)	880 (51%)	719 (51%)
Alemtuzumab	157 (8%)	146 (8%)	136 (10%)
Other/Unknown	437 (23%)	369 (21%)	298 (21%)
Smoking status, n (%)			
Current	158 (8%)	140 (8%)	123 (9%)
Former	590 (31%)	534 (31%)	400 (28%)
Never	914 (48%)	820 (48%)	675 (48%)
Unknown	253 (13%)	228 (13%)	212 (15%)
Characteristics assessed during baseline period (6-12 mo posttransplant)			
Baseline serum bicarbonate (mEq/L), mean (SD)	24.5 (2.8)	24.6 (2.8)	24.5 (2.8)
Baseline eGFR (mL/min/1.73 m^2), mean (SD)	60.6 (32.6)	63.4 (31.5)	63.3 (33.8)
Maximum eGFR (mL/min/1.73 m^2), mean (SD)	70.4 (36.3)	73.2 (35.1)	73.1 (37.7)
CKD stage, n (%)			
Stage 1	220 (11%)	209 (12%)	182 (13%)
Stage 2	618 (32%)	596 (35%)	479 (34%)
Stage 3a	525 (27%)	500 (29%)	389 (28%)
Stage 3b	318 (17%)	281 (16%)	219 (16%)
Stage 4	135 (7%)	100 (6%)	88 (6%)
Stage 5	99 (5%)	36 (2%)	53 (4%)
Systolic blood pressure, n (%)			
<120 mm Hg	364 (19%)	337 (20%)	289 (20%)
120–132 mm Hg	535 (28%)	474 (28%)	397 (28%)
133–144 mm Hg	464 (24%)	409 (24%)	314 (22%)
>144 mm Hg	327 (17%)	288 (17%)	228 (16%)
Blood pressure data missing	225 (12%)	214 (12%)	182 (13%)
Diastolic blood pressure, n (%)			
<70 mm Hg	562 (29%)	490 (28%)	377 (27%)
70-78 mm Hg	580 (30%)	522 (30%)	416 (30%)
79-85 mm Hg	358 (19%)	331 (19%)	279 (20%)
>85 mm Hg	190 (10%)	165 (10%)	156 (11%)

(Continued)

Table 1 (Cont'd). Demographics and Clinical Characteristics of the Study Cohort

	Overall Study Cohort (N = 1,915)[a]	Graft Failure Study Cohort (N = 1,722)	MACE+ Study Cohort (N = 1,410)
Maintenance immunosuppression, n (%)[b]			
Tacrolimus	1,603 (84%)	1,479 (86%)	1,196 (85%)
Mycophenolate sodium	316 (17%)	300 (17%)	216 (15%)
Mycophenolate mofetil	1253 (65%)	1150 (67%)	942 (67%)
Cyclosporine	69 (4%)	59 (3%)	36 (3%)
Characteristics assessed for one year posttransplant			
ACE inhibitors or ARBs prescription, n (%)[b]	525 (27%)	464 (27%)	366 (26%)
Diuretics prescription, n (%)**	764 (40%)	671 (39%)	515 (37%)
History of new onset diabetes, n (%)	228 (12%)	206 (12%)	160 (11%)
History of posttransplant infection, n (%)	1,330 (69%)	1,171 (68%)	938 (67%)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate (calculated by the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation); MACE+, major adverse cardiovascular event; SD, standard deviation.
[a]Mortality and hospitalization were assessed in overall study cohort.
[b]Evaluated for 12 months, beginning 6 months posttransplant

failure during the first year posttransplant were excluded; and 1,915 in the all-cause mortality and hospitalization outcomes group, which had no exclusions for preindex events (Table 1).

Demographic and clinical characteristics were similar across all outcome-specific cohorts (Table 1) as well as within cohort among patients whose bicarbonate increased, was unchanged, or decreased (Tables S2-S4 and S9). The mean age ranged from 49-51 years, approximately 40% were female, and approximately half had diabetes. In each outcome-specific cohort, approximately 45% of the cohort was a race or ethnicity other than non-Hispanic White: approximately 24% of patients were Black, 14% were Hispanic, and approximately 7% were Asian. The ratio of deceased donors to living donors was 2:1 and approximately 28% of patients had received a prior kidney transplantation.

The mean baseline eGFR ranged from 60.6-63.4 mL/min/1.73 m^2 across the outcome cohorts; most patients were in CKD stage 2 (35%) or stage 3 (45%) and few were in stage 5 (2%). The mean baseline serum bicarbonate was approximately 24.5 mEq/L across the outcome cohorts and 17% of patients had a serum bicarbonate <22 mEq/L.

Among patients with a serum bicarbonate <22 mEq/L, 14%, 16%, 25%, 23%, 19%, and 2% were in CKD stages 1, 2, 3a, 3b, 4, and 5, respectively. Baseline characteristics of all study cohorts are summarized by baseline serum bicarbonate ranges in Tables S5-S7. The distribution of baseline serum bicarbonate in the study population is summarized in Fig S1 and Table S8.

Graft Failure

A total of 674 (39%) KTRs experienced graft failure during the outcome period with a median and maximum follow-up of 2.6 years and 10 years, respectively. Adjusted Cox proportional hazards models showed that each 1 mEq/L increase in serum bicarbonate over time and 1 mEq/L higher baseline serum bicarbonate were both associated with reduced hazard of graft failure after adjusting for multiple covariates (hazard ratio [HR], 0.90; 95% confidence interval [CI], 0.87-0.92; $P < 0.001$ and HR, 0.95; 95% CI, 0.92-0.98; $P < 0.001$, respectively) (Fig 3 and Table 2). Of the other covariates included in the Cox proportional hazards models, living donor (vs deceased donor) and higher baseline eGFR, were strongly associated with a reduced hazard of graft failure (both $P < 0.001$), whereas prior transplantation and Black race (vs non-Hispanic White) were strongly associated with an increased hazard of graft failure ($P = 0.005$ and $P = 0.004$, respectively) (Table S4). Because our definition of graft failure included death with a functioning transplant, we also analyzed death as a competing risk; the observed relationships between serum bicarbonate (both change in serum bicarbonate over time and baseline serum bicarbonate) and graft failure remained significant in this analysis (Table S15). We found similar relationships in another sensitivity analysis that excluded patients with baseline serum bicarbonate ≥ 30 mEq/L (Table S10).

All-Cause Mortality

At total of 246 (13%) KTRs died during the outcome period with a median and maximum follow-up of 2.4 years and 10 years, respectively. Adjusted Cox proportional hazards models showed that each 1 mEq/L increase in serum bicarbonate over time and each 1 mEq/L higher baseline serum bicarbonate were associated with reduced hazard of death after adjusting for multiple covariates (HR, 0.92; 95% CI, 0.88-0.96; $P < 0.001$ and HR, 0.94; 95% CI, 0.90-0.99; $P = 0.03$, respectively) (Fig 3 and Table 2). Of the covariates included in the Cox proportional hazards models, higher baseline eGFR (but not higher maximum eGFR) was associated with reduced hazard of death ($P < 0.001$), whereas the only other variable strongly associated with a higher hazard of death was older age

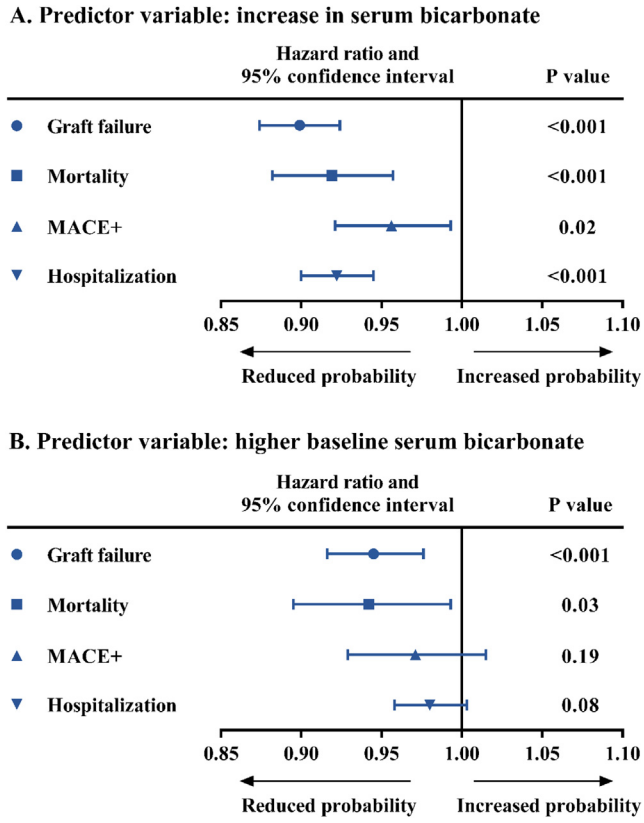

Figure 3. Effects of rising serum bicarbonate and higher baseline serum bicarbonate on graft failure, mortality, MACE+, and hospitalization. **A. Change in serum bicarbonate.** Each 1 mEq/L increase in serum bicarbonate significantly reduced the risk of graft failure (HR, 0.90; 95% CI, 0.87-0.92; $P < 0.001$), death (HR, 0.92; 95% CI, 0.88-0.96; $P < 0.001$), MACE+ (HR, 0.96; 95% CI, 0.92-0.99; $P = 0.02$), and first hospitalization (HR, 0.92; 95% CI, 0.90-0.95; $P < 0.001$). **B. Baseline serum bicarbonate**. Each 1 mEq/L higher baseline serum bicarbonate significantly reduced the risk of graft failure (HR, 0.95; 95% CI, 0.92-0.98; $P < 0.001$) and death (HR, 0.94; 95% CI, 0.90-0.99; $P = 0.03$) but not MACE+ or first hospitalization. Abbreviations: CI, confidence interval; HR, hazard ratio; MACE+, major adverse cardiovascular event.

($P < 0.001$) (Table S4). We found similar relationships in a sensitivity analysis that excluded patients with baseline serum bicarbonate ≥ 30 mEq/L (Table S11).

Major Adverse Cardiac Events

A total of 349 (25%) KTRs experienced a MACE+ during the outcome period with a median and maximum follow-up of 2.5 years and 10 years, respectively. Adjusted Cox proportional hazards models showed that rising serum bicarbonate over time was associated with a reduced hazard of MACE+ after adjusting for multiple covariates (HR, 0.96; 95% CI, 0.92-0.99; $P = 0.02$). Baseline serum bicarbonate, however, was not significantly associated with MACE+ (Fig 3 and Table 2). We found similar relationships in a sensitivity analysis that excluded patients with baseline serum bicarbonate ≥ 30 mEq/L (Table S12).

Hospitalization

During the first full year after the index date, 787 (41%) KTRs were hospitalized at least once and the total number of hospitalizations during this period was 1,713. Between > 1 year and 3 years after the index date, 710 (37%) patients had been hospitalized at least once. Adjusted Cox proportional hazards models showed that rising serum bicarbonate over time was associated with a reduced hazard of hospitalization after adjusting for multiple covariates (HR, 0.92; 95% CI, 0.90-0.95; $P < 0.001$). Baseline serum bicarbonate, however, was not significantly associated with hospitalization (Fig 3 and Table 2). We found similar relationships in a sensitivity analysis that excluded patients with baseline serum bicarbonate ≥ 30 mEq/L (Table S13).

Additional Sensitivity Analyses

To further examine the effect of rising serum bicarbonate on graft failure, MACE+, hospitalization, and death among patients with normal or high baseline serum bicarbonate, we examined potential interactions between baseline serum bicarbonate (low [12 to < 22 mmol/L], normal [≥ 22 to < 30 mmol/L], and high [≥ 30 mmol/L]) and changes in serum bicarbonate. There were no significant interactions for graft failure, MACE+, or hospitalization for any comparison (Table S14). For death, there was no significant interaction in the comparison between the baseline low and high serum bicarbonate groups; however, the interaction for the comparison between baseline low and normal serum bicarbonate groups for this endpoint was significant.

DISCUSSION

In this large US community-based diverse cohort of KTRs with a median follow-up of approximately 2.5 years, we found that rising serum bicarbonate was associated with a reduced hazard for graft loss and adverse patient outcomes. Specifically, each 1 mEq/L increase in serum bicarbonate was associated with a lower hazard of graft loss, all-cause mortality, major cardiovascular events, and hospitalization by 10%, 8%, 4%, and 8%, respectively, independent of demographics, baseline eGFR, use of angiotensin-converting enzyme inhibitor and angiotensin receptor blockers, donor type, prior transplantation, immunosuppression, blood pressure, diabetes status, and other comorbid conditions. Additionally, the association of rising serum bicarbonate with a lower hazard of graft loss was consistent after adjusting for death as a competing risk (Table S15).

Based on prior findings that incidence of graft loss was lowest in patients whose 3-month posttransplant serum bicarbonate level was between 26-28 mEq/L,[10] we chose to examine the effects of changes in serum bicarbonate in a population of patients with a range of baseline serum bicarbonate levels and not just in those bicarbonate levels below the normal range.

Table 2. Adjusted Cox Proportional Hazards Models for Graft Failure, Mortality, MACE+, and Hospitalization

	Time-Dependent Change From Baseline in Posttransplant Serum Bicarbonate, per 1-mEq/L Increase		Baseline Serum Bicarbonate, per 1 mEq/L Increase	
Outcome	HR (95% CI)	*P*	HR (95% CI)	*P*
Graft failure	0.90 (0.87-0.92)	<0.001	0.95 (0.92-0.98)	<0.001
Mortality	0.92 (0.88-0.96)	<0.001	0.94 (0.90-0.99)	0.03
MACE+	0.96 (0.92-0.99)	0.02	0.97 (0.93-1.02)	0.19
Hospitalization	0.92 (0.90-0.95)	<0.001	0.98 (0.96-1.00)	0.08

Note: Data from other variables included in the model are shown in Table S8.
Abbreviations: CI, confidence interval; HR, hazard ratio; MACE+, major adverse cardiovascular event.

We established a posttransplantation baseline period for a number of variables including serum bicarbonate, eGFR, blood pressure, and relevant concomitant medications as the most relevant baseline rather than using a pretransplant period when a number of these factors would have been affected by dialysis. We chose the change in serum bicarbonate over time as our primary predictor variable (rather than baseline serum bicarbonate) to better emulate the potential effects of therapeutic interventions to increase the serum bicarbonate and to make use of multiple serum bicarbonate measures over time (rather than just 1 or 2 baseline measurements) in our time-dependent Cox proportional hazards models. We did evaluate baseline serum bicarbonate as a secondary independent variable and found that it also was associated with graft loss and all-cause mortality. The findings from our primary outcomes (graft failure and mortality) are consistent with those from a multicenter study of KTRs from South Korea that reported a significant association between metabolic acidosis with total CO_2 <22 mEq/L 3 months posttransplant with an increased risk of graft loss and mortality.[10] Our study replicated their findings in a large US community-based population, reflecting the racial and ethnic diversity of the US kidney transplant population. Furthermore, our study extended their findings by quantifying the incremental risk-reduction associated with each 1 mEq/L increase in serum bicarbonate.

Our findings suggest that rising serum bicarbonate even among patients with serum bicarbonate in the normal range was associated with better outcomes. The optimal serum bicarbonate that is associated with better outcomes may be in the upper end of the normal range. Kovesdy et al[13] found an incremental hazard reduction between serum bicarbonate values between 22 mEq/L and 28 mEq/L for the composite endpoint of predialysis mortality or end-stage kidney disease in the general CKD population. The physiological basis for this may be that serum bicarbonate declines late in the course of acid retention because it is maintained for a period of time by mechanisms that are maladaptive in the long-term (eg, bone demineralization and increased acid excretion per remaining nephron). Thus, rising serum bicarbonate in patients with normal baseline serum bicarbonate may represent the adequate replenishment of previously depleted blood and bone buffers and reduced energy demands on remaining nephrons.[5]

We found that rising serum bicarbonate, but not baseline serum bicarbonate, was significantly associated with future MACE+ (de novo stroke, myocardial infarction, heart failure; heart failure hospitalization in patients with a history of heart failure; and cardiovascular death). Djamali et al[11] using a somewhat different set of cardiovascular outcomes that included arrhythmias and procedures for ischemic events in a cohort of KTRs from the University of Wisconsin, found that metabolic acidosis (total CO_2 <20 mEq/L) 1 year posttransplant was a significant predictor of increased risk of cardiovascular events. Due to the differences in outcome measures and the study population, direct comparisons cannot be made with our study, but both studies found an association of low serum bicarbonate with increased cardiovascular risk in KTRs. Compared with the University of Wisconsin population, our study population had a higher proportion of non-Hispanic Whites (45% vs 20%), a lower proportion of recipients of living donor transplants (25% vs 41%), and somewhat higher proportion of patients that had been retransplanted (27% vs 20%). Our observed associations of reduced MACE+ outcomes with rising serum bicarbonate are consistent with similar observations in the community-based CKD population.[14]

Patients with CKD retain acid due to a reduced nephron mass that is unable to produce sufficient ammonia to excrete acid from dietary sources and metabolism. Importantly, the degree of tubular injury at any given level of eGFR is an important determinant of the ability to handle an acid load. Unlike the CKD population in which there is a monotonic increase in the prevalence of metabolic acidosis from CKD stage 2 through stages 4 and 5,[15] we found that the proportion of KTRs with a serum bicarbonate <22 mEq/L was similar among those with CKD stages 3a, 3b, and 4 (25%, 23%, and 19%, respectively) and that the prevalence of serum bicarbonate <22 mEq/L among patients with CKD stages 2 and 3a posttransplant was higher than would be expected based on data from the National Health and Nutrition Examination Survey CKD population (16% vs 8% for CKD stage 2 and 29% vs 9% for CKD stage 3a). These findings are consistent with the previously described high prevalence of renal tubular

acidosis in KTRs and prevalent transplant-specific etiologies of tubular injury, including calcineurin inhibitor toxicity, acute rejection, and ischemia.[16]

Identification of treatable risk factors that can slow graft loss and improve patient outcomes is critical to maximizing the public health and individual patient benefits that can be reaped from the limited number of organs available for transplantation. Our study shows that rising serum bicarbonate, even in small increments (eg, 1 mEq/L) is associated with improved graft and patient survival. Cardiovascular events are the leading cause of death among KTRs.[17] The reduced mortality associated with rising serum bicarbonate was likely due, in part, to the reduction in MACE+. It would be expected that reducing the risk of graft loss and cardiovascular events should reduce hospitalization. This expectation was borne out by our analysis of hospitalizations.

In multiple randomized, controlled trials, treatment of patients with CKD and metabolic acidosis slowed progression of CKD and/or improved composite outcomes of death, dialysis, or eGFR decline.[18-23] However, no studies to date have examined the effects of correcting acidosis on graft function in KTRs.

Our study has a number of strengths. To our knowledge, this is the largest study of community-based KTRs to evaluate the effects of metabolic acidosis in this population. Although generalizability to the US population of KTRs cannot be confirmed, it is strengthened by the fact that the population was drawn from nearly 900,000 patients with eGFR <60 mL/min/1.73 m^2 and concurrent serum bicarbonate measurements who were, in turn, drawn from a pool of over 103 million patients from all 50 United States with all insurance types and insurance statuses. We used both diagnostic and procedure codes to identify graft failure and cardiovascular outcomes and social security records to ascertain deaths. Our primary predictor variable, time-dependent change from baseline in serum bicarbonate, utilized all available bicarbonate values after 1 year posttransplant and before outcomes during a median follow-up of approximately 2.5 years, rather than just 1 or 2 baseline measurements.

Limitations of the study include that it was observational and thus, despite adjustment for multiple covariates, the possibility of residual confounding exists. Further, although the database we used was large and included many health care systems and physician practices across all US regions, it is theoretically possible for patients to move to a health care system that did not partner with Optum, potentially leading to missed outcomes. This dataset was derived from a well-recognized EHR data repository and not from a transplant center or centers. As such, we did not have data on donor characteristics or detailed recipient characteristics and matching, but we included data on induction and maintenance immunosuppression. We did not capture all interventions that affect serum bicarbonate longitudinally including over-the-counter sodium bicarbonate use and dietary changes. In previous studies in nontransplant patients, however, use of sodium bicarbonate among patients with metabolic acidosis was very low.[12] As this was not an interventional study, our findings of the association of rising serum bicarbonate with better graft and patient outcomes do not necessarily reflect benefit of treatment, particularly because the literature suggests that only a small fraction of patients with CKD receive treatment for metabolic acidosis.[12,21] Finally, although in the setting of chronically low serum bicarbonate in an outpatient with CKD is most likely to represent metabolic acidosis, rather than another acid-base disorder, we acknowledge that some patients with low serum bicarbonate may not have had metabolic acidosis.

In conclusion, we found that in a US community-based population of KTRs even small incremental increases in serum bicarbonate (1 mEq/L) were significantly associated with reduced hazard of graft loss, all-cause mortality, cardiovascular events, and hospitalization. The findings from our study, when taken together with the work of others,[10,11] point to the need for well-designed interventional studies evaluating the effect of treating metabolic acidosis in KTRs.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1: Distribution of baseline serum bicarbonate in the study population.

Table S1: Sources, Measurements, and Definitions.

Table S2: Baseline Characteristics of Graft Failure Study Cohort by Serum Bicarbonate Change Categories.

Table S3: Baseline Characteristics of MACE+ Study Cohort by Serum Bicarbonate Change Categories.

Table S4: Adjusted Cox Proportional Hazards Models for Graft Failure, Mortality, MACE+, and Hospitalization (All Variables) Variable.

Table S5: Baseline Characteristics of Overall Study Cohort by Baseline Serum Bicarbonate.

Table S6: Baseline Characteristics of Graft Failure Study Cohort by Baseline Serum Bicarbonate.

Table S7: Baseline Characteristics of MACE+ Study Cohort by Baseline Serum Bicarbonate.

Table S8: Numbers of Patients by Baseline Serum Bicarbonate Category Within Each Outcome-Specific Cohort.

Table S9: Baseline Characteristics of Overall Study Cohort by Serum Bicarbonate Change Categories.

Table S10: Adjusted Cox Proportional Hazards for Graft Failure, Omitting Patients With Baseline Serum Bicarbonate ≥ 30 mEq/L.

Table S11: Adjusted Cox Proportional Hazards for All-Cause Mortality, Omitting Patients With Baseline Serum Bicarbonate ≥ 30 mEq/L.

Table S12: Adjusted Cox Proportional Hazards for MACE+, Omitting Patients With Baseline Serum Bicarbonate ≥ 30 mEq/L.

Table S13: Adjusted Cox Proportional Hazards for Inpatient Admissions, Omitting Patients With Baseline Serum Bicarbonate ≥ 30 mEq/L.

Table S14: Hazard Ratios per 1-mEq/L Increase in Serum Bicarbonate Over Time Evaluated at Baseline Serum Bicarbonate

Categories, From Sensitivity Analyses Using Time-Dependent Cox Proportional Hazard Models With Interaction Terms and Stratified Cohort Models.

Table S15: Adjusted Fine and Gray Model for Graft Failure With Death as Competing Risk.

ARTICLE INFORMATION

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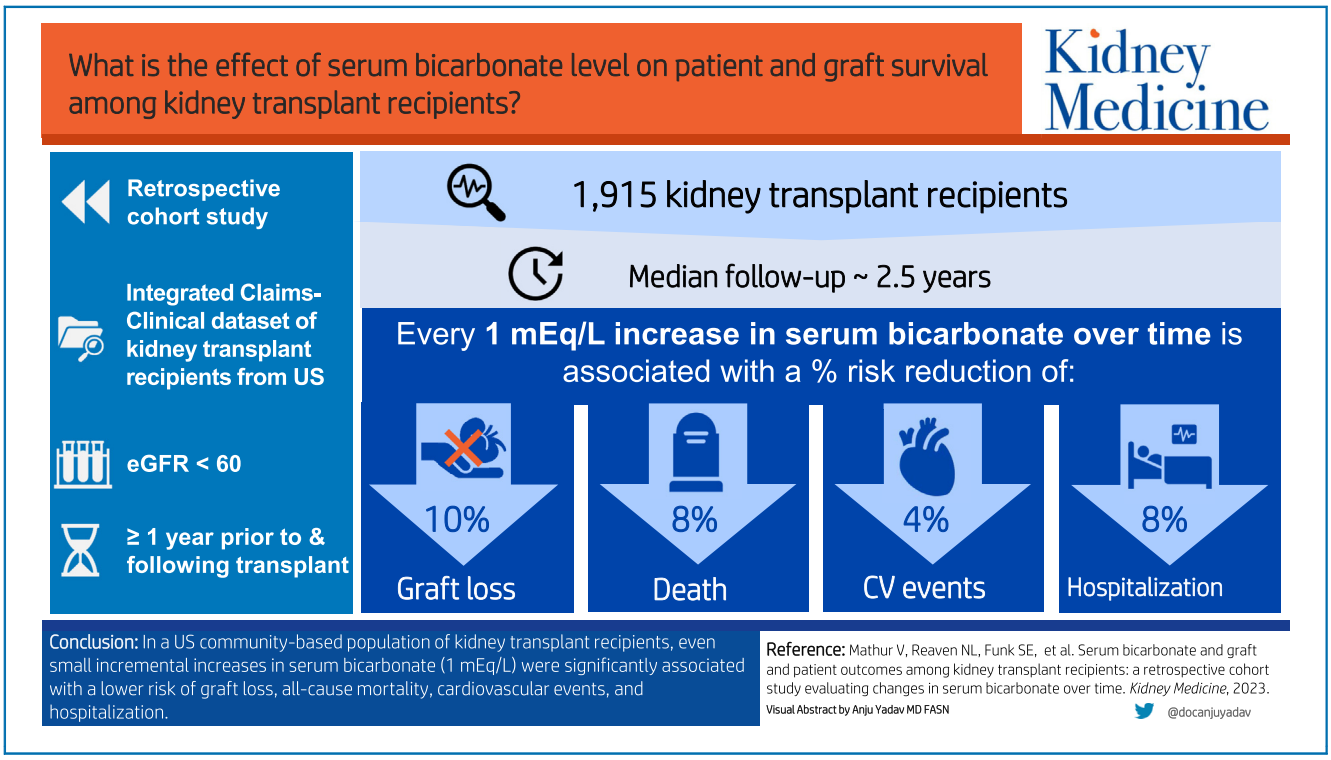
What is the effect of serum bicarbonate level on patient and graft survival among kidney transplant recipients?
Kidney Medicine
Retrospective cohort study
Integrated Claims-Clinical dataset of kidney transplant recipients from US
eGFR < 60
≥ 1 year prior to & following transplant
1,915 kidney transplant recipients
Median follow-up ~ 2.5 years
Every 1 mEq/L increase in serum bicarbonate over time is associated with a % risk reduction of:
10%
Graft loss
8%
Death
4%
CV events
8%
Hospitalization
Conclusion: In a US community-based population of kidney transplant recipients, even small incremental increases in serum bicarbonate (1 mEq/L) were significantly associated with a lower risk of graft loss, all-cause mortality, cardiovascular events, and hospitalization.
Reference: Mathur V, Reaven NL, Funk SE, et al. Serum bicarbonate and graft and patient outcomes among kidney transplant recipients: a retrospective cohort study evaluating changes in serum bicarbonate over time. Kidney Medicine, 2023.
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