Urine Complement Factor Ba Identifies Persistent Acute Kidney Injury and Organ Failures in Critically Ill Adults

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Introduction: Critically ill adults with acute kidney injury (AKI) have high morbidity and mortality and lack treatment options. We assessed the association between complement activation (urine Ba fragment levels), and AKI and organ failures.

Methods: A biorepository of critically ill adults was leveraged. AKI staging was based on the Kidney Disease Improving Global Outcomes serum creatinine (sCr) criteria. AKI recovery was defined as sCr reduction to <0.3 mg/dl above baseline within 48 hours after AKI diagnosis. Persistent AKI was defined as need for renal replacement or no sCr recovery. Urine was obtained at intensive care unit (ICU) admission, and at 12 and 24 hours after admission; and urine Ba levels were quantitated via enzyme-linked immunosorbent assay and natural log transformed. Regression analyses were performed to test the association between urine Ba and organ failure outcomes. We adjusted for age and the acute physiology and chronic health evaluation II (APACHE-II) score, which is used to classify ICU severity of illness.

Results: A total of 439 patients were included: 252 without AKI, 124 with stage 1 AKI, 43 with stage 2 AKI, and 20 with stage 3 AKI. After adjusting for covariates, urine Ba increased as AKI stage increased. Urine Ba was higher in patients with persistent AKI compared with patients with AKI recovery and without AKI. Increased urine Ba was associated with worse organ failure outcomes (fewer ventilator, ICU, and inotrope-free days, and fewer days alive).

Conclusion: Urine Ba is increased in patients with severe AKI and discriminates between patients who have AKI recovery and patients who develop persistent AKI. A doubling of urine Ba was associated with a 6.6-fold increased odds of persistent AKI. Future studies to validate these findings and to trial complement factor B inhibition are warranted.

AKI in critically ill adults is a heterogeneous syndrome that is independently associated with high morbidity and mortality. Patients who survive have higher rates of chronic kidney disease progression, cardiovascular events, and mortality.[1] Other than supportive care, there are no treatment options likely because of multifactorial etiology. Further, sCr is used

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as gold standard for diagnosis; however, it is a delayed marker of renal injury and cannot distinguish between fluid-responsive prerenal AKI and persistent AKI.[2] The identification of other biomarkers could lead to more personalized therapy options and targeted prognostic enrichment into future clinical trials.

The complement cascade is part of the innate immune system, and emerging evidence identifies complement activation fragments,[3-8] as potential AKI biomarkers. Complement proteins, especially factor B, have been implicated in the pathogenesis of numerous primary kidney diseases, and there is emerging evidence of its role in AKI in critically ill adults and children.[3,6,8-11] Factor B is integral in the alternative pathway's amplification loop, which leads to increased

generation of complement factors (anaphylatoxins C3a, C5a, and membrane attack complex C5b-9) that cause damage via sublytic effects and lysis of cells.[9,12,13] Urine Ba is a complement activation fragment that reflects factor B activation either because of systemic inflammation and filtration of complement proteins and/or localized tubular complement activation. In adults with AKI after cardiac surgery, urine Ba, a marker of alternative pathway activation, increased proportional to AKI severity and before the increase in sCr.[3] In critically ill children, urine Ba increased as AKI severity increased,[8] had the highest levels in AKI from sepsis,[4,5] and was increased up to 24 hours before sCr elevation.[7]

The aim of this study was to determine the association between urine Ba and organ failures, including AKI, in a large cohort of critically ill adults. We hypothesized that urine Ba would be able to discriminate between patients without AKI, patients who had AKI recovery, and patients with persistent AKI for over 48 hours. Further we hypothesized the higher urine Ba values would be associated with higher AKI severity and other organ failures as defined by days free from intensive care, ventilatory support, and/or inotropic support.

METHODS

Patient Identification

An ancillary study was performed using a biorepository developed through the EARLYARF Trial. This trial was a double-blind placebo-controlled trial studying the effect of early erythropoietin on prevention of AKI development in critically ill adults.[14] The study was approved by the Multiregional Ethics Committee of New Zealand (MEC/050020029) and registered under the Australian New Zealand Clinical Trials Registry (ACTRN012606000032550). The study was conducted in adherence to the Institutional Review Board and Declaration of Helsinki standards. Details of inclusion and exclusion criteria, consent, sample collection, and urine biomarker analysis are well-described.[14-16] In brief, eligible patients were critically ill adults with expected ICU length of stay > 24 hours, survival > 72 hours, did not have a 3 times increase in sCr at ICU admission, were not anuric, not on renal replacement therapy or expected to require within 48 hours, had no signs of hematuria or rhabdomyolysis, and were not receiving chemotherapy. ICU severity of illness was estimated using the APACHE-II score; and the sequential organ failure assessment score, the ICU measure of organ function or rate of failure.

AKI Classification and Diagnosis

The Acute Kidney Injury Network sCr definition of AKI was used for AKI diagnosis; it is an absolute increase in sCr ≥ 0.3 mg/dl or an increase ≥50% within 48 hours.[17] Daily sCr was obtained for 7 days. For patients (49% of cohort) without baseline sCr before admission, the lowest of the on-admission, final ICU, or follow-up sCr was determined as baseline; this approach has been previously well-validated.[16,18] Patients without AKI for 72 hours of admission served as the control group (no-AKI). Renal recovery was defined as sCr reduction to <0.3 mg/dl above baseline within 24 or 48 hours after AKI diagnosis. Persistent AKI was defined as no recovery within 48 hours after AKI diagnosis or need for renal replacement therapy.

Outcomes

For the initial trial and this *post hoc* analysis, the primary outcome of interest was the stage of AKI, which was defined using sCr Kidney Disease Improving Global Outcomes criteria.[19] Secondary outcomes of interest included persistent AKI, days alive, and organ failure–free days. Information on organ failures was available for up to 14 days after ICU admission and included ICU-free days, invasive ventilator–free days, and inotrope-free days. Only patients who survived the first 14 days were included in the organ failure–free days analysis.

Urine Biomarker Analysis

Urine was obtained on ICU admission and at 12 and 24 hours post admission. Urine samples were stored at −80 °C until batch analysis for previous urinary biomarker analysis (cystatin C, KIM-1, IL-18, and uNGAL[16]). Levels of Ba in urine were measured using commercially available enzyme-linked immunosorbent assays validated for clinical diagnostics (Quidel, San Diego, CA). Urine Ba values (ng/ml) were measured at multiple time points depending on biospecimen availability. The coefficient of variation of interassay reproducibility is 3.4% and for intraassay reproducibility is 2.2%. A proportion of measurements were made in duplicate, and all were in a blinded fashion.

Statistical Analysis

Because previous analyses showed that erythropoietin had no effect on AKI outcomes, this analysis combines both treatment (erythropoietin) and placebo arms. Admission characteristics between groups were compared using 1-way analysis of variance, Kruskal-Wallis rank sum test, and Fisher exact test. Because urine Ba was not normally distributed, it was natural log transformed. The mean value (including admission, 12 hours, and 24 hours) was used in logistic and linear

regression analyses. Logistic regression analyses were performed to test the strength of the association between urine Ba values and AKI stages, and covariates were prespecified and included age and APACHE-II score. Additional logistic regression analyses adjusted for these same covariates and tested the association between urine Ba and persistent AKI. Linear regression was performed to test the association between urine Ba and organ failure measurements, both on univariate analysis and multivariate analysis. Subanalyses were performed to determine the association between urine Ba and persistent AKI development in 2 subpopulations. The first group comprised patients with AKI diagnosed on admission. The second group comprised patients admitted without AKI, which encompassed patients who never had AKI and patients who developed AKI within 24 to 48 hours after admission.

RESULTS

Of the original 528 patients enrolled, 439 patients had available biospecimens and clinical information and were included in this study. Of those, 252 (57%) had no AKI, 123 (28%) had AKI at ICU admission, and 64 (15%) developed AKI at 24 to 48 hours after ICU admission (Figure 1). Of those who had AKI on admission, 63 (51%) had persistent AKI, whereas 60 (49%) had AKI recovery within 48h. Similar proportions were observed in patients who developed AKI at 24 hours or 48 hours after ICU admission.

Admission demographics are shown in Table 1. Patients who developed stage 3 AKI tended to be younger (average of 57.4 ± 17.4 years) compared with patients who developed stage 1 AKI (64.3 ± 16.9 years) ($P = 0.008$). Patients who developed stage 3 AKI had higher APACHE-II score (median: 22.1; interquartile range [IQR]: 17.5–27.5) compared with patients without AKI

(median: 16.8; IQR: 13–20) ($P < 0.001$). Patients with stage 3 AKI had higher estimates of illness severity using overall sequential organ failure assessment score, and the respiratory and cardiovascular subscores.

On univariate analysis, patients with stage 3 AKI had worse organ failures compared with patients without AKI (Table 2). There was no difference in mortality rate. On average, patients with stage 3 AKI had 2 fewer days free from ventilator support (8.2 days; IQR: 5.8–12.3) compared with patients without AKI (10.3 days; IQR: 8–13) ($P = 0.037$). Patients with stage 3 AKI also had over 2.5 fewer days free from inotrope support (8.9 days; IQR: 7.8–12) compared with patients without AKI (11.6 days; IQR: 12–14) ($P < 0.001$). Finally, patients with stage 3 AKI had 2.5 fewer ICU-free days (6.9 days; IQR: 5–10.3) compared with patients without AKI (9.5 days; IQR: 7–13) ($P = 0.001$). There were no significant differences between patients with stage 1 or 2 AKI and patients without AKI.

Urine Ba increased stepwise as AKI stage increased at multiple time points after adjusting for age and APACHE-II scores (Figure 2). A similar pattern was observed after adjusting urine Ba values for urine creatinine values (Supplementary Tables S1 and S2). Patients with stage 3 AKI had significantly higher urine Ba than patients without AKI at all time points: ICU admission (average ln_urine Ba: 6.5 ± 2.5 vs. 4.7 ± 2.2; $P = 0.0004$), 12 hours after admission (average ln_urine Ba: 7.3 ± 1.2 vs. 4.8 ± 2.1; $P < 0.0001$), and 24 hours after admission (average ln_urine Ba: 7.4 ± 0.9 vs. 5.1 ± 1.9; $P < 0.0001$). Urine Ba in patients with stage 2 AKI was significantly higher than urine Ba from patients without AKI at all time points: ICU admission (average ln_urine Ba: 6.0 ± 2.1; $P = 0.0013$), 12 hours (average: 6.1 ± 2.5; $P = 0.0036$), and 24 hours (average: 6.5 ± 2.5; $P = 0.0009$). Similarly, urine Ba was higher in patients with stage 1 compared with no AKI: ICU
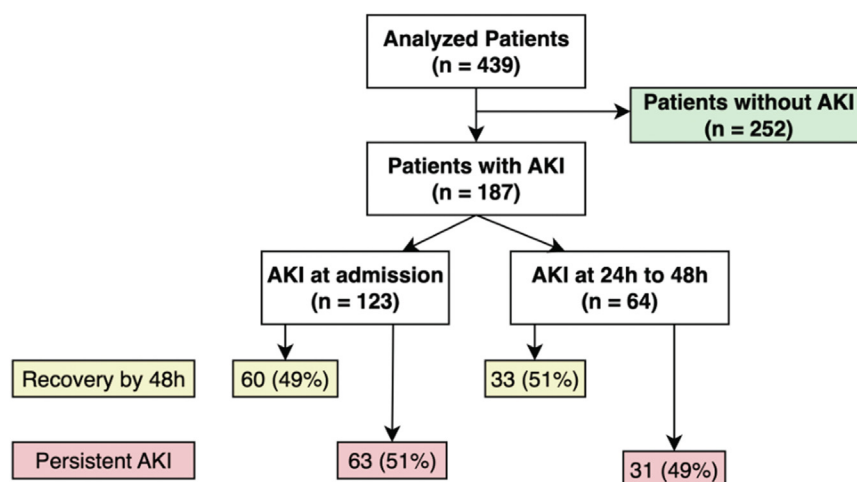

Figure 1. Consort diagram showing number of patients included in the study and AKI diagnoses. AKI, acute kidney injury.

Table 1. Demographics of included patients

Variable	Overall N = 439	No AKI N = 252	Stage 1 AKI N = 124	Stage 2 AKI N = 43	Stage 3 AKI N = 20	P-value
Admission characteristics						
Age, mean (SD), yr	60.4 (17.1)	58.3 (17.5)	64.3 (16.9)	63.2 (14.2)	57.4 (17.4)	0.008[a]
Baseline plasma creatinine	0.85 (0.68–1.04)	.79 (.68–1.02)	.95 (.77–1.17)	.79 (.68–1.02)	.79 (0.67–.90)	NS
APACHE-II	17.9 (13–21)	16.8 (13–20)	19.0 (15–22)	18.8 (16–21)	22.1 (17.5, 27.5)	<0.001[a]
Overall SOFA	6 (4–8)	5 (4–7)	7 (5–8)	8 (6–9)	9 (6–11)	<0.001[a]
SOFA Respiratory	2 (1–3)	2 (1–3)	2 (2–3)	3 (2–3)	3 (1.9–3.3)	<0.001[a]
SOFA Cardiovascular	1 (0–3)	1 (0–3)	2 (0–4)	3 (1–4)	3 (1–4)	<0.005[b]
Admission category						<0.005[b]
Abdominal Surgery	81 (18.5%)	37 (14.8%)	24 (19.4%)	14 (32.6%)	6 (30%)	
Trauma/burn	43 (9.8%)	31 (12.4%)	10 (8%)	1 (2%)	1 (5%)	
Cardiac	134 (30.7%)	78 (31.2%)	42 (33.9%)	11 (25.6%)	3 (15%)	
Neurologic	60 (13.7%)	45 (18%)	12 (9.7%)	1 (2.3%)	2 (10%)	
Sepsis	26 (6%)	7 (2.8%)	14 (11.3%)	2 (4.7%)	3 (15%)	
Pulmonary	89 (20.4%)	49 (19.6%)	22 (17.7%)	13 (30.2%)	5 (25%)	

AKI, acute kidney injury; APACHE-II: Acute Physiology and Chronic Health Evaluation II; an ICU severity of illness classification; ICU, intensive care unit; IQR, interquartile range; SOFA, sequential organ failure assessment score; and ICU measure of organ function or rate of failure.
[a]One-way analysis of variance.
[b]Fisher exact test.
Mean (SD) or median (IQR) are shown.

admission (average: 5.7 ± 2.1; $P = 0.0007$), 12 hours (average: 5.9 ± 1.9; $P = 0.0005$), and 24 hours (average: 6.0 ± 2.2; $P = 0.0009$). At 12 hours, there was a significant difference between stage 1 and 3 AKI ($P = 0.0022$) and stage 2 and 3 AKI ($P = 0.015$). At 24 hours, the difference between stage 1 and 3 AKI persisted ($P = 0.0023$) as did the difference between stage 2 and stage 3 ($P = 0.0015$).

The ability to differentiate between patients with persistent AKI compared with AKI recovery and no AKI was then assessed (Figure 3). After adjusting for age and APACHE-II score, urine Ba was significantly higher in patients who developed persistent AKI compared with patients with AKI recovery or no AKI. At ICU admission, urine Ba was highest in patients who developed persistent AKI (average ln_urine Ba: 6.1 ± 2.1) compared with patients with AKI recovery (average ln_urine: 5.3 ± 2.4; $P = 0.002$) and patients without AKI (average ln_urine: 4.7 ± 2.1; $P < 0.0001$). Similar differences were observed at 12 hours: persistent AKI (average ln_urine: 6.5 ± 1.7) was higher than AKI recovery (average ln_urine 5.5 ± 2.3; $P = 0.004$) and no AKI (average ln_urine: 4.8 ± 2.1; $P < 0.0001$) and also at 24 hours after ICU admission: persistent AKI

(average ln_urine: 6.6 ± 1.9) was higher than AKI recovery (average ln_urine: 5.7 ± 2.3; $P = 0.01$) and no AKI (average ln_urine: 5.1 ± 1.9; $P < 0.0001$).

Multivariate analysis was performed to predict persistent AKI (Table 3). Because persistent AKI could not be diagnosed until at least 48 hours after ICU admission, all 3 time points (admission, 12 hours, and 24 hours) were used in these analyses. After adjustment for age and APACHE-II score, urine Ba was associated with an almost 7-fold increased odds of persistent AKI (odds ratio: 6.6; 95% confidence interval [CI]: 1.5–29.6; $P = 0.013$). Subanalysis showed that in patients admitted with AKI and after adjusting for age and APACHE-II score, urine Ba was associated with increased odds of developing persistent AKI (odds ratio: 1.30; 95% CI 1.043–1.613; $P = 0.019$). Similarly, in patients admitted without AKI and after adjusting for age and APACHE-II score, urine Ba was associated with increased odds of developing persistent AKI (odds ratio: 1.37; 95% CI 1.06–1.77; $P = 0.015$).

The association between mean urine Ba and organ failures was also investigated (Table 4). A higher mean urine Ba was associated with fewer days alive (estimate:

Table 2. Univariate outcomes of interest based on AKI staging

Outcomes of Interest	Overall N = 439	No AKI N = 252	Stage 1 AKI N = 124	Stage 2 AKI N = 43	Stage 3 AKI N = 20	P-value
Ventilator-free days	10 (7–13)	10.3 (8–13)	10.1 (7–13)	10.9 (7–12.5)	8.2 (5.8–12.3)	0.037[a]
Inotrope-free days	11.4 (11–14)	11.6 (12–14)	11.4 (11–13.3)	11.0 (10–13)	8.9 (7.8–12)	<0.001[a]
ICU-free days	9.3 (7–12)	9.5 (7–13)	9.6 (7–12)	8.7 (7–11)	6.9 (5–10.3)	0.001[a]
Mortality (%)	17.8%	18.6%	16.1%	16.3%	20%	0.9[b]

AKI, acute kidney injury; ICU, intensive care unit, IQR, interquartile range.
[a]Kruskal-Wallis rank sum test.
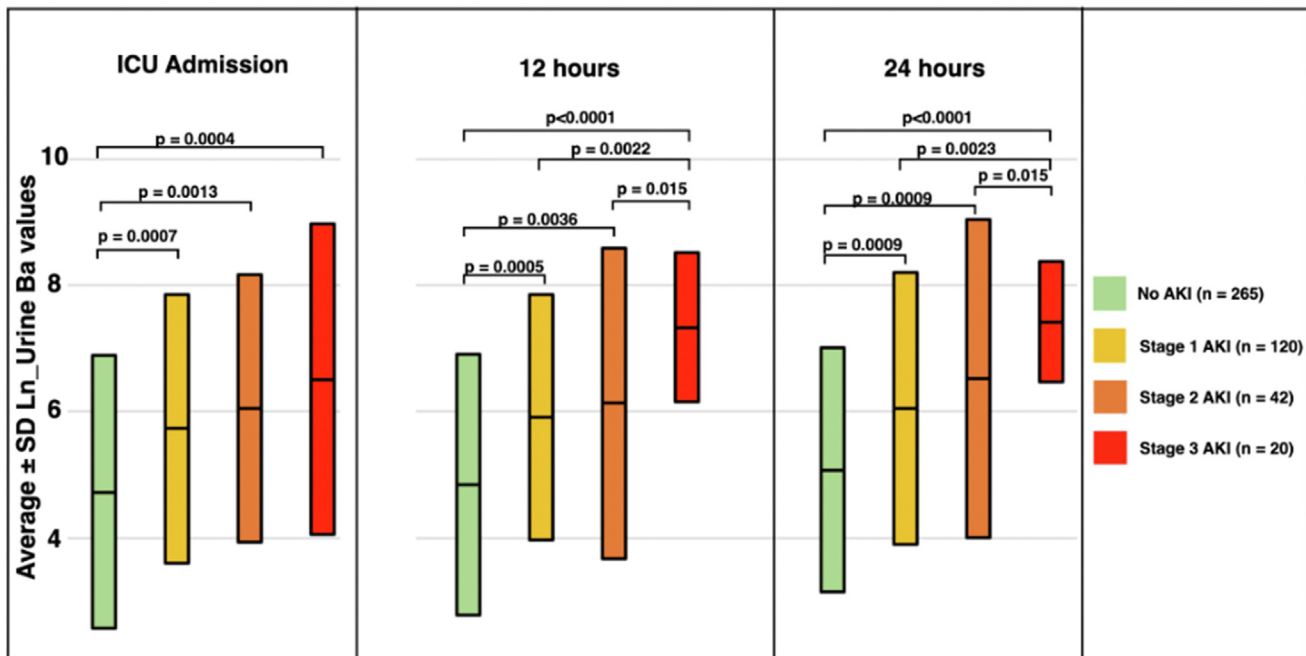[b]Fisher exact test.
Mean (IQR), n (%) are shown.

Figure 2. Urine Ba values and AKI staging. Average and SDs of Ln_Urine Ba values are shown based on AKI staging. Multiple time points are shown, including ICU admission, 12 hours after admission, and 24 hours after admission. There were significant differences between patients without AKI compared with patients with AKI at all timepoints. AKI, acute kidney injury; ICU, intensive care unit.

0.71; 95% CI: 0.56–0.88; $P = 0.0025$), fewer ventilator-free days (estimate: 0.75; 95% CI: 0.60–0.93; $P = 0.008$), fewer inotrope-free days (estimate: 0.76; 95% CI: 0.62–0.92; $P = 0.004$), and fewer ICU-free days (estimate: 0.74; 95% CI: 0.60–0.91; $P = 0.005$).

DISCUSSION

This is the first study that examined urine complement B fragments in critically ill adults in a moderately sized, heterogeneous cohort. Urine Ba increased in a stepwise fashion as AKI severity increased and
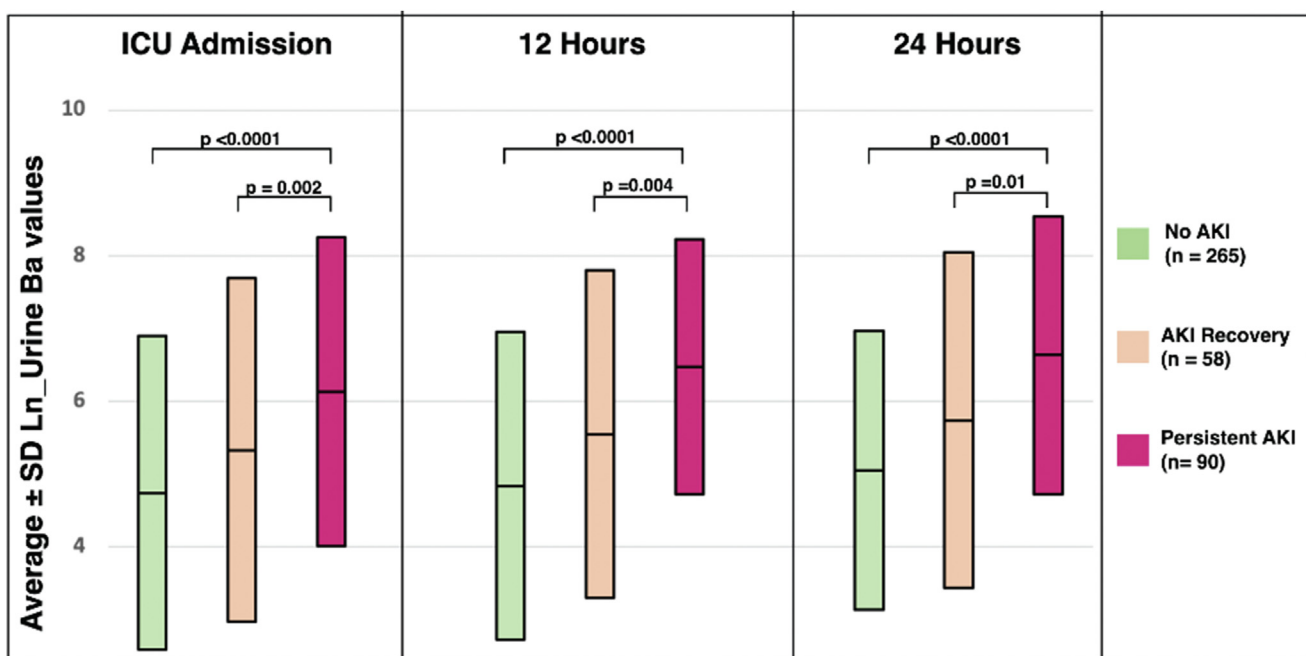

Figure 3. Urine Ba values and AKI persistence. Average and SDs of Ln_Urine Ba values are shown based on persistent of AKI. Multiple time points are shown, including ICU admission, 12 hours after admission, and 24 hours after admission. There were significant differences between patients who developed persistent AKI compared with patients who had AKI recovery and no AKI. AKI, acute kidney injury; ICU, intensive care unit.

Table 3. Prediction of persistent AKI by urine Ba

Population Included	Model	Odds ratio (95% CI)	P-value
Entire cohort	Urine Ba unadjusted	5.7 (1.5–29.6)	0.02
	Urine Ba adjusted[a]	6.6 (1.5–29.6)	0.013
AKI at admission	Urine Ba unadjusted	1.29 (1.04–1.61)	0.02
	Urine Ba adjusted[a]	1.30 (1.04–1.61)	0.019
No AKI at admission	Urine Ba unadjusted	1.39 (1.10–1.77)	0.0069
	Urine Ba adjusted[a]	1.37 (1.06–1.77)	0.015

AKI, acute kidney injury; APACHE-II: Acute Physiology and Chronic Health Evaluation II; an ICU severity of illness classification; CI, confidence interval; ICU, intensive care unit.
[a]Adjusted for age and APACHE-II score.
Urine Ba from all 3 time points (admission, 12 hours, 24 hours) included.

patients who had persistent AKI had higher urine Ba values compared with patients who had AKI recovery. In patients with similar age and illness severity, a doubling of urine Ba was associated with a 6.6-fold increased odds of persistent AKI. Urine Ba therefore may function as both a biomarker and mediator of AKI in critically ill adults.

Our findings add to previous preliminary evidence demonstrating the association between urine Ba and AKI severity, although this is the first large study to evaluate this in a heterogeneous cohort of critically ill adults. In adults after cardiac surgery, urine Ba levels associated with AKI severity and dialysis use.[3] This association was also observed in pediatric patients after cardiac surgery, as well as heterogeneous cohorts of critically ill children with and without sepsis.[4,5,7,8] This is also the first study that used urine Ba values to discriminate between AKI that recovers within 48 hours and persistent AKI. This opens the possibility of using urine Ba to help guide management of these patients. For example, in patients with urine Ba values suggesting AKI recovery, they may benefit from further fluid resuscitation. Alternatively, patients with urine Ba suggesting persistent AKI development may benefit from conservative fluid resuscitation, increased optimization of hemodynamics, and avoidance of nephrotoxins. Although there was some overlap between these 2 groups, this study lays the groundwork for future studies that discern between those with likely AKI recovery and those who will develop persistent AKI.

Table 4. Prediction of organ failure outcomes by mean urine Ba

Outcome of interest	Predictor	Estimate	95% CI	P-value
Days alive	Urine Ba	0.73	0.58–0.92	0.007
	Urine Ba adjusted[a]	0.71	0.56–0.88	0.0025
Ventilator-free days	Urine Ba	0.77	0.61–0.96	0.02
	Urine Ba adjusted[a]	0.75	0.60–0.93	0.008
Inotrope-free days	Urine Ba	0.73	0.60–0.89	0.002
	Urine Ba adjusted[a]	0.76	0.62–0.92	0.004
ICU-free days	Urine Ba	0.74	0.60–0.92	0.0062
	Urine Ba adjusted[a]	0.74	0.60–0.91	0.0050

APACHE-II: Acute Physiology and Chronic Health Evaluation II; an ICU severity of illness classification; CI, confidence interval; ICU, intensive care unit.
[a]Adjusted for age and APACHE-II score.

Although activation of complement has been implicated in specific diseases causing organ failures, this is the first study that evaluated the association with urine Ba and organ failure days in a heterogeneous cohort of critically ill adults. In adults with heart failure, worse disease severity was noted in patients with elevated plasma factor B levels,[20] and decreased plasma factor H, which is the primary negative regulator of the alternative pathway.[21] In adults with acute respiratory distress syndrome, patients who died had lower plasma factor H and higher plasma factor B activation compared with survivors.[22] In conjunction with these other studies, our findings suggest that an excessively activated alternative complement pathway is associated with organ failures.

In addition to this growing clinical evidence of the role of the alternative pathway of complement in AKI pathogenesis, there is robust preclinical evidence. In 2 mouse models of sepsis and ischemia-reperfusion injury, complement factor B (-/-) mice (which cannot activate the alternative pathway) demonstrated improved survival, attenuated kidney tissue damage, and lower AKI biomarkers levels (NGAL and KIM-1).[23,24] Further, complement factor B (-/-) mice had improved cardiac function.[23] In addition, mice after sepsis or ischemia-reperfusion injury had improved survival and attenuated AKI after treatment with a direct factor B inhibitor.[25,26] In rat models of glomerular disease, a factor B inhibitor prevented tubular degeneration.[27] The results of our study in addition to the previous clinical and preclinical evidence provide increasing motivation for future clinical trials evaluating complement-targeted therapeutics in critically ill patients.

Despite the evidence of complement factor B involvement in the pathogenesis of AKI and other organ failures, we were unable to distinguish between systemic and localized tubulointerstitial activation as the cause of these organ failures. Based on previous kidney biopsy tissues and animal models, we hypothesize that localized tubulointerstitial complement activation is the driving factor of AKI development and reflected in urine Ba measurements. In patients with acute tubular necrosis and chronic kidney disease, biopsy tissues show that localized tubulointerstitial activation is involved in the interstitial damage.[28] Kidney biopsies from patients with chronic kidney disease showed high expression of factor B and factor C3 in tubulointerstitium compared with healthy controls.[29] In animal models of acute tubular necrosis,[28] the alternative pathway was necessary for complement tubular deposition and similar deposition was seen in biopsy tissue from patients with acute tubular necrosis. However, we were unable to determine if

systemic activation is contributing to elevated urine Ba values because of the absence of plasma biospecimens that would allow for measurement of systemic complement activation. Future studies of complement activation should evaluate both systemic and localized tubulointerstitial activation simultaneously.

Our study has some limitations. First, it was designed *post hoc* and performed on urine samples that were collected 15 years ago. However, the samples had been frozen and stored appropriately and the pattern of elevation was similar to urine Ba elevation in prior pilot studies[3,4,7,8] as well as other studies in differing diseases such as focal segmental glomerulosclerosis[11] and transplant-associated thrombotic microangiopathy.[30] The pattern of elevation also corresponded with elevation of previously measured biomarkers, including urine NGAL and KIM-1.[16] Owing to the age of the specimens, we did not correct for proteinuria because previous studies showed variable decline in levels of albumin and microproteins with long-term storage.[31,32] We were only able to include 14 days of organ failure information based on the available database and were unable to evaluate major adverse kidney events at either 30 or 90 days because of the absence of data. Finally, because most patients had AKI upon admission to the ICU, we were unable to use urine Ba to predict AKI at admission.

Our study also has multiple strengths. This is the first study to compare urine Ba and AKI severity and persistence in critically ill adults. In addition, this is the first study to evaluate urine Ba and organ failures in critically ill adults, which should be validated in additional studies. Our findings are consistent with both preclinical studies and smaller studies of critically ill children and further strengthen the association between urine Ba and AKI severity in critically ill patients.

In summary, we found that urine Ba increases as AKI severity and other organ failure outcomes worsen. Further, urine Ba can distinguish between persistent AKI and AKI that recovers. Thus, urine Ba shows potential for prognostic enrichment in future clinical trials evaluating AKI treatments. Severe urine Ba elevation may identify which critically ill patient may benefit from factor B inhibition, which is currently being evaluated in clinical trials for other diseases. Overall, our study calls for further investigation into complement-mediated AKI and identification of cutoff values that may aid in planning for future clinical trials of factor B inhibition.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Average urine Ba/urine creatinine values based on AKI staging.

Table S2. Average urine Ba/urine creatinine values based on AKI persistence or recovery.

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