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Original Article

Dipstick albuminuria and acute kidney injury recovery in critically ill septic patients

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SUMMARY AT A GLANCE

In a study of 988 patients admitted with with septic AKI in ICU, the authors show that dipstick positive albuminuria is associated with a low rate of recovery at 30 days.

ABSTRACT:

Aim: **Acute kidney injury (AKI) is a frequent complication of sepsis, a pro-inflammatory state that alters tubular handling of filtered albumin. We hypothesized that dipstick albuminuria (DA) is associated with a lower rate of AKI recovery in septic patients.**

Methods: **This was a single-centre, retrospective cohort study of adults with sepsis-associated AKI in an urban academic intensive care unit (ICU). Patients with unknown baseline serum creatinine (SCr), absent urinalysis, and those with estimated glomerular filtration rate (eGFR) <15 mL/min per 1.73m^2 or receiving chronic renal replacement therapy (RRT) were excluded. The independent variable was DA (negative or trace, 30 mg/dL, and ≥100 mg/dL) within the first 72 h of ICU stay. The outcome variable was AKI recovery at 30 days following hospital discharge, defined as the last SCr returning to a level less than 1.5 times the baseline SCr level and independence of RRT.**

Results: **A total of 988 patients were included in the study. The median length of hospitalization was 11 days. The patients with higher degree of DA had worse critical illness scores. After adjustment for several confounders, DA ≥30 mg/dL was independently associated with "no AKI recovery" at 30 days post-discharge (adjusted OR 1.40, 95% CI, 1.01–1.95 for DA =30 mg/dL and 1.67, 1.15–2.42 for DA ≥100 mg/dL, $P = 0.02$). Other independent predictors of "no AKI recovery" were cumulative fluid balance, Sequential Organ Failure Assessment (SOFA) score, exposure to diuretics, and the need for mechanical ventilation.**

Conclusion: **Dipstick albuminuria ≥30 mg/dL is independently associated with lower rate of AKI recovery at 30 days post-discharge. Our findings emphasize the potential utility of a simple routine test of DA in the risk-stratification of AKI recovery in ICU septic patients.**

Disclosure
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Author contributions:
JAN, JY, and RDT conceived and designed the study. JAN was responsible for data collection. JAN, LY, and RDT were responsible for primary analysis and interpretation of data. XL and BAH carried out the statistical analysis and helped to revise the manuscript. JAN drafted the manuscript. JAN, LY, JY, and RDT revised the manuscript for important intellectual content. JAN, JY, and RDT were responsible for administrative, technical, and material support. JAN supervised the study. All authors read and approved the final manuscript.

Sepsis is common in the intensive care unit (ICU) and confers high morbidity and mortality.[1,2] Acute kidney injury (AKI) is a frequent complication of sepsis[3,4] and is present in over half of all patients with septic shock.[5]

Sepsis is an imbalanced pro-inflammatory state that leads to endothelial dysfunction.[6,7] Glomerular albuminuria is thought to be a manifestation of this enhanced capillary leak[8] that could be augmented by the occurrence of AKI. Experimental ischaemic and toxic AKI have demonstrated alterations in glomerular structure and function;[9] impairment in proximal tubular albumin reabsorption;[10] and postulated possible enhancement of tubular albumin secretion.[11]

Semi-quantitative albuminuria, measured by urinary dipstick, is widely available in the initial evaluation of septic patients. Dipstick albuminuria (DA) has shown promise in the prediction of contrast-induced AKI[12] and AKI following cardiac surgery.[13] We previously reported the independent association between *de novo* DA and severe AKI in septic patients.[14] However, the value of DA for risk-stratification of AKI recovery is not known. Therefore, the primary aim of this study was to investigate whether the presence of DA is reflective of more severe underlying glomerular or tubular dysfunction, which influences AKI recovery in critically ill septic patients who suffered from AKI. We hypothesized that the presence of DA is associated with a lower rate of AKI recovery in this susceptible population.

METHODS

Study design and participants

We conducted a single-centre, retrospective cohort study using an administrative-linked electronic database of patients admitted to the ICU in an urban academic medical centre. Study participants were identified from ICU admissions with a primary diagnosis of severe sepsis or septic shock from May 2007 to April 2012. Severe sepsis or septic shock was defined by Angus criteria,[1] using International Classifications of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for both a bacterial or fungal infection and a diagnosis of acute organ dysfunction excluding gastrointestinal failure. We included adult patients who suffered from sepsis-associated AKI, defined by serum creatinine (SCr)-based Kidney Disease: Improving Global Outcomes (KDIGO) criteria.[15] Baseline SCr was determined by the most recent SCr within the 3-month period before ICU admission. The highest SCr within 72 h of admission was used to adjudicate AKI. Patients with unknown baseline serum creatinine (SCr), absent urinalysis within the first 72 h of ICU stay, and those with estimated glomerular filtration rate (eGFR) <15 mL/min per 1.73m^2 or receiving chronic renal replacement therapy (RRT) were excluded. The study was approved by the Institutional Review Board (IRB #7044).

Study variables

A single-measurement dipstick urinalysis within the first 72 h of ICU stay was used to determine DA status. If more than one urinalysis was performed, the highest degree of DA was used to adjudicate DA status. Semi-quantitative DA results ranged from negative to 600 mg/dL (AUTION, Sticks 9EB, Arkray USA, Edina, MN, USA). DA results were analyzed as ordinal data in three categories: negative or trace, 30 mg/dL, and $\geq$100 mg/dL. Baseline SCr was used to calculate baseline eGFR using the four-variable Modification of Diet in Renal Disease (MDRD) study equation.[16] Cumulative fluid balance (CFB) was calculated based on total fluid input minus output within the first 72 h of ICU stay. The Acute Physiology and Chronic Health Evaluation II (APACHE-II)[17] and Sequential Organ Failure Assessment (SOFA)[18] scores were calculated with data from the first day of ICU admission. Comorbidities were identified using ICD-9-CM codes. Data pertaining to nephrotoxin exposure, need for vasoactive drugs (pressor or inotrope), diuretic use, red blood cell transfusion, mechanical ventilation, and length of hospitalization were based on hospital billing codes for the indexed admission within the time frame of the study.

Study outcomes

The primary outcome measure, AKI recovery, was defined as the return of the last SCr during the observation period to a level less than 1.5 times (50% above) the baseline SCr level and RRT-independence (Fig. 1). This definition has been previously reported in literature.[19–21] The use of acute RRT was identified using hospital billing codes for the indexed observation period by data management personnel blinded to the study. The observation period lasted from ICU admission until 30 days following hospital discharge or death, whichever occurs first.

Statistical analysis

Categorical data were reported as frequencies and percentages and continuous data as means ± SD or median [IQR]. Between-group comparisons of DA status for categorical variables were made using χ^2 test. For continuous variables, one-way ANOVA or Kruskal–Wallis test (if data were non-Gaussian distributed) was used. Multivariable logistic regression models were constructed for "no AKI recovery" as the dependent variable and three-category DA (negative or trace, 30 mg/dL, and $\geq$100 mg/dL) as the main independent variable. Candidate variables for the multivariable models included demographic data (age, gender, and race); comorbidities (baseline SCr, diabetes, hypertension, and anaemia); indicators of critical illness (SOFA and APACHE-II scores, CFB at 72 h, mechanical ventilation, red blood cell transfusion, and length of hospital stay); and drug exposure (diuretic and intravenous or intra-arterial iodine contrast). Length of hospital stay was dichotomized

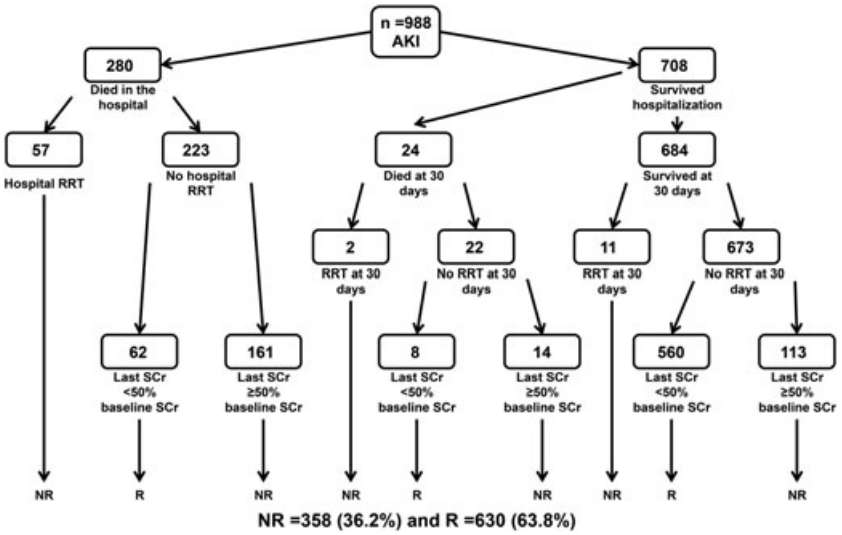

Fig. 1 Study cohort and acute kidney injury (AKI) recovery outcome adjudication algorithm. NR, no AKI recovery; R, AKI recovery; RRT, acute renal replacement therapy; SCr, serum creatinine.

as ≥ vs < median value of 11 days. Inclusion into the final model was based on significance of univariable results and clinical relevance. Only one of two variables was included in the event of collinearity between variables. Jonckheere-Terpstra test for trend was used to compare the ratio of last SCr/baseline SCr among the three ordinal DA categories; the worst rank was given to those who were on RRT at the end of the observation period. Kaplan–Meier curves were constructed for time-to-AKI recovery among the three DA categories and differences were compared by log-rank trend test. The 95% confidence intervals (CI) reported for the logistic regression odds ratios (ORs) were based on Wald estimation. Two-sided *P*-values <0.05 indicated statistical significance. SAS 9.4 (SAS Institute, Cary, NC, USA) was used for statistical analysis.

Sensitivity analysis

To further validate our results, we performed a sensitivity analysis in which "no AKI recovery" was adjudicated for every patient that died during the observation period ($n = 304$), independent of the ratio of last SCr/baseline SCr or RRT-independence.

RESULTS

Clinical characteristics

Among 1535 critically ill septic patients admitted to the ICU, 988 (64.4%) suffered from AKI and were included in the study. Of the 988 patients with AKI, 136 required acute RRT during the hospitalization. Of these 136 patients, 59 (43.4%) died, 11 (8.1%) were RRT-dependent, and 66 (48.5%) were RRT-independent at the end of the observation period. A total of 304 out of 988 (30.8%) AKI patients died during the observation period (30 days post-discharge) (Fig. 1).

Among patients with AKI, DA was negative or trace in 320 (32.4%), 30 mg/dL in 419 (42.4%), and ≥100 mg/dL in 249 (25.2%). About 75% of patients with severe AKI (KDIGO stage ≥2) had DA ≥30 mg/dL. Clinical characteristics of the study cohort are reported in Table 1. Patients with higher degree of DA had higher admission SOFA and APACHE-II scores and CFB at 72 h ($P < 0.001$ for all). The median length of hospital stay in the entire cohort was 11, IQR [6 – 20] days.

Study outcomes

Association of DA with AKI recovery

Of 988 patients who suffered from AKI, 519 (52.5%) had mild AKI (KDIGO stage 1) and 469 (47.5%) had severe AKI (KDIGO stage ≥2). Fifty-five percent of patients with DA ≥100 mg/dL and 62% of those with DA =30 mg/dL recovered from AKI. In contrast, 73% of those with DA negative or trace recovered from AKI ($P < 0.001$ when compared to 60% of those with DA ≥30 mg/dL who recovered from AKI). Baseline and peak SCr comparisons by DA status are illustrated in Table 2. The mean ratio of last SCr / baseline SCr among the three DA categories (negative or trace, 30 mg/dL, and ≥100 mg/dL) exhibited a direct response relationship with higher degree of DA as shown in Fig. 2: 2.01 (95%CI 1.73–2.3) for DA negative or trace, 2.31 (2.04–2.58) for DA =30 mg/dL, and 2.61 (2.24–2.97) for DA ≥100 mg/dL, *P* for trend <0.001.

The presence of DA was associated with "no AKI recovery" at 30 days following hospital discharge (OR 1.61, 95% CI, 1.18 – 2.21 for DA =30 mg/dL vs negative or trace and 2.12, 1.49 – 3.01 for DA ≥100 mg/dL vs negative or trace, $P < 0.001$). After adjustment for several potential confounders (age, gender, race, comorbidities, SOFA score, CFB at 72 h, mechanical ventilation, red blood cell transfusion, drug exposure, and length of hospital stay), DA remained independently associated with "no AKI recovery" (adjusted OR 1.40,

Table 1 Patient characteristics by dipstick albuminuria (DA) status in 988 patients with sepsis-associated acute kidney injury (AKI)

	DA negative or trace *n* = 320	DA =30 mg/dL *n* = 419	DA ≥100 mg/dL *n* = 249	*P*-value*
Demographics				
Age, years, mean ± SD	64.9 ± 16.0	65.5 ± 16.4	64.2 ± 15.3	0.61
Men, *n* (%)	175 (54.7)	227 (54.2)	138 (55.4)	0.88
Race, *n* (%)				
Black	129 (40.3)	183 (43.7)	126 (50.6)	0.18
White	127 (39.7)	155 (37.0)	79 (31.7)	
Other	64 (20.0)	81 (19.3)	44 (17.7)	
Comorbidity				
Baseline SCr, mg/dL, median [IQR]	1.20 [0.90, 1.50]	1.10 [0.80, 1.40]	1.20 [0.90, 1.60]	0.03
Baseline eGFR, mL/min per 1.73m^2, median [IQR]	63.5 [44.7, 82.9]	67.6 [47.6, 92.0]	63.4 [47.5, 87.8]	0.10
Diabetes, *n* (%)	71 (22.2)	86 (20.5)	64 (25.7)	0.37
Anaemia, *n* (%)	276 (87.3)	371 (89.0)	204 (82.6)	0.13
Hypertension, *n* (%)	139 (43.4)	168 (40.1)	97 (39.0)	0.27
Systolic heart failure, *n* (%)	18 (5.6)	16 (3.8)	5 (2.0)	0.02
Drug exposure				
Diuretics, *n* (%)	164 (51.3)	174 (41.5)	108 (43.4)	0.04
Iodine contrast, *n* (%)	70 (21.9)	89 (21.2)	73 (29.3)	0.05
Aminoglycoside, *n* (%)	28 (8.8)	43 (10.3)	22 (8.8)	0.92
Statin, *n* (%)	109 (34.1)	104 (24.8)	73 (29.3)	0.15
Critical illness indicators				
LOS, days, median [IQR]	10 [6, 18]	12 [6, 21]	12 [7, 19]	0.26
Mechanical ventilation, *n* (%)	130 (40.6)	193 (46.1)	129 (51.8)	0.008
Blood transfusion, *n* (%)	10 (3.1)	11 (2.6)	13 (5.2)	0.21
SOFA score, median [IQR]	4 [2, 8]	5 [3, 8]	6 [4, 9]	<0.001
APACHE II score, median [IQR]	12 [8, 16]	13 [9, 18]	14 [10, 20]	<0.001
CFB 72 h, litres, mean ± SD	3.22 ± 6.85	6.02 ± 7.15	6.66 ± 7.87	<0.001
Pressor or inotrope, *n* (%)	139 (43.4)	177 (42.2)	116 (46.6)	0.49

Anaemia, haematocrit <39% for men and <36% for women; APACHE II, Acute Physiology and Chronic Health Evaluation II; CFB 72 h, cumulative fluid balance (total fluid input minus output within the first 72 h of ICU stay); eGFR, estimated glomerular filtration rate based on Modification of Diet in Renal Disease (MDRD) study equation; iodine contrast only if intravenous or intra-arterial; LOS, length of hospital stay; SCr, serum creatinine; SOFA, Sequential Organ Failure Assessment. * χ^2 test for categorical variables and ANOVA (Gaussian data) or Kruskal–Wallis test (non-Gaussian data) for continuous variables.

Table 2 Acute kidney injury (AKI) recovery at 30 days following hospital discharge stratified by dipstick albuminuria (DA) status

	DA negative or trace *n* =320	DA =30 mg/dL *n* =419	DA ≥100 mg/dL *n* =249	*P*-value*
Baseline SCr, mg/dL, median [IQR]	1.20 [0.90, 1.50]	1.10 [0.80, 1.40]	1.20 [0.90, 1.60]	0.03
Peak SCr, mg/dL, median [IQR]	2.10 [1.50, 3.20]	2.30 [1.60, 3.30]	2.70 [1.80, 4.20]	<0.001
30-day AKI recovery, n (%)[†]	232 (72.5)	260 (62.1)	138 (55.4)	<0.001
LOS, days, median [IQR]	10 [6, 18]	12 [6, 21]	12 [7, 19]	0.26

[†]AKI recovery defined as the return of the last SCr during the observation period to a level less than 1.5 times (50% above) the baseline SCr level and RRT-independence; LOS, length of hospital stay; *χ^2 test for categorical variable and Kruskal–Wallis test for continuous variables

1.01–1.95 for DA = 30 mg/dL vs negative or trace and 1.67, 1.15–2.42 for DA ≥100 mg/dL vs negative or trace, $P = 0.02$). In our multivariable model, other important predictors related to AKI recovery at 30 days post-discharge were CFB at 72 h, SOFA score, exposure to diuretics, and the need for mechanical ventilation (Table 3).

Concordantly, time-to-AKI recovery was significantly different among the three DA categories and exhibited an indirect response relationship between higher degree of DA and AKI recovery (log-rank *P* for trend = 0.002) (Fig. 3).

Sensitivity analysis

The study outcome of "no AKI recovery" was adjudicated for every patient that died during the observation period ($n = 304$), independent of the ratio of last SCr / baseline SCr or RRT-independence in the sensitivity analysis. The results of this analysis were similar: OR for the association between DA and "no AKI recovery" 1.48, 1.09 –1.99 for DA =30 mg/dL vs negative or trace and 1.94, 1.38–2.72 for DA ≥100 mg/dL vs negative or trace, $P < 0.001$.

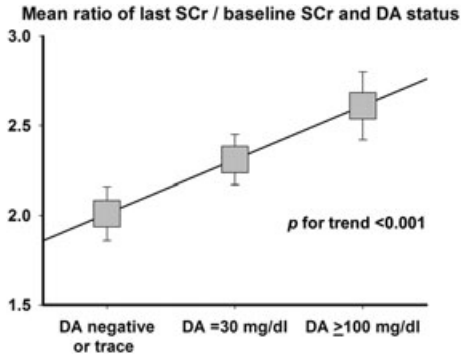

Fig. 2 Mean ratio of last serum creatinine (SCr) by baseline SCr (Y axis) plotted against 3-category dipstick albuminuria (DA) (X axis). Square box indicates the mean ± SE (error bar). *P*-value for trend <0.001 by Jonckheere-Terpstra test.

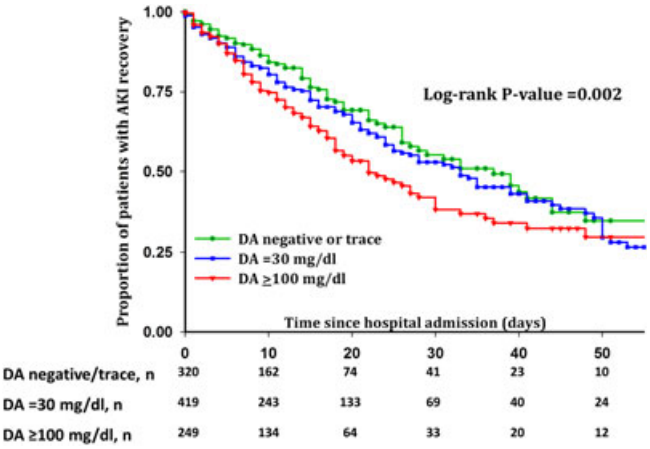

Fig. 3 Kaplan–Meier plot of the association of 3-category dipstick albuminuria (DA) with AKI recovery at 30 days following hospital discharge. Log-rank *P*-value for trend = 0.002.

DISCUSSION

The main new finding in our study is that the presence of dipstick albuminuria ≥30 mg/dL is independently associated with lower rate of AKI recovery at 30 days post-discharge in ICU septic patients who suffered from AKI. Our findings suggest that a simple routine test to semi-quantitatively identify albuminuria could be a useful marker for the risk-stratification of AKI recovery in ICU septic patients. This is important because the duration of AKI directly impacts long-term survival and increases the risk of chronic kidney disease post-AKI.[22,23] Therefore, DA may also help guide appropriate evaluation and management after hospital discharge.[24] In addition, we described phenotypic differences among AKI patients with different degrees of DA within the first 72 h of ICU stay. Finally, our observations suggest an indirect relationship between higher degree of DA and AKI recovery that may reflect more severe glomerular or tubular damage and less plausible AKI recovery with higher degree of DA.

The early detection of AKI may promote timely intervention and mitigate kidney damage.[25,26] However, AKI is a complex and heterogeneous syndrome without standardized diagnostic or prognostic biomarkers.[27] In this context, the comprehensive use of the routinely performed urinalysis has gained recognition.[28,29] As a component of the conventional urinalysis, DA is becoming a "red flag" in the assessment of AKI. In a small retrospective cohort of trauma patients who received intravenous contrast, the strongest predictor of contrast-induced AKI was albuminuria measured by dipstick.[12] Similarly, DA was independently associated with the development of AKI in critically ill patients with sepsis or severe burns.[14,30] Furthermore, early postoperative albuminuria improved the prediction of AKI in patients undergoing cardiac surgery. Specifically, DA ≥100 mg/dL was associated with greatest risk for AKI.[13] In critically ill patients, increasing microalbuminuria in the first 48 h of ICU admission had a high negative predictive value for the development of AKI and multiple organ failure.[31]

Possible causes of albuminuria in sepsis-associated AKI

Sepsis is a systemic inflammatory state. A very early feature of inflammation in sepsis is endothelial dysfunction and increased capillary permeability to plasma proteins.[32,33] While

Table 3 Multivariable analysis of "no AKI recovery" as the dependent variable and 3-category dipstick albuminuria (DA) status (negative or trace, 30 mg/dL, and ≥100 mg/dL) as the main independent variable

Clinical variables	Adjusted OR	95% CI	*P*-value	Model C-statistic (95% CI)
DA ≥100 mg/dL vs negative or trace	1.67	1.15 – 2.42	0.02	0.69 (0.65 – 0.72)
DA ≥30 mg/dL vs negative or trace	1.40	1.01 – 1.95		
CFB 72 h, per 1 L increase	1.05	1.03 – 1.08	<0.001	
SOFA score, per 1 unit increase	1.08	1.03 – 1.12	<0.001	
Diuretic exposure, yes vs no	1.36	1.02 – 1.82	0.04	
Mechanical ventilation, yes vs no	1.46	1.07 – 2.00	0.02	

Candidate variables for the multivariable models included demographic data (age, gender, and race); comorbidities (baseline SCr, diabetes, hypertension, and anaemia); indicators of critical illness (SOFA and APACHE-II scores, CFB at 72 h, mechanical ventilation, red blood cell transfusion, and length of hospital stay); and drug exposure (diuretic, and intravenous or intra-arterial iodine contrast). Length of hospital stay was dichotomized as ≥ vs < median value of 11 days. Inclusion into the final model was based upon significance of univariable results (*P*-value <0.05) and clinical relevance. Only 1 of 2 variables was included in the event of collinearity between variables. CFB 72 h = cumulative fluid balance (total fluid input minus output within the first 72 h of ICU stay); CI, confidence interval; SOFA, Sequential Organ Failure Assessment score.

the nature of albuminuria in patients with sepsis is incompletely understood, one possibility is that albuminuria occurs as a result of enhanced glomerular capillary permeability due to inflammatory mediators.[8] In addition, alterations in proteins integral to the glomerular barrier could play a role in albuminuria in this setting. In this regard, in a mouse model of septic AKI, Kato and colleges[34] identified a decreased amount of podocin and tensin 2 that are essential for podocyte structure and function. The downregulation of these proteins was associated with foot process effacement and albuminuria after 36 h of injury.

Recent experimental AKI models have been used to investigate the tubular contribution to the occurrence of albuminuria in AKI. These observations described impaired albumin reabsorption and possibly enhanced albumin secretion. Schreiber and coworkers[10] demonstrated that acute endotoxaemia and ischaemia-reperfusion-mediated AKI in mice induced the downregulation of the multi-ligand receptors, megalin and cubilin, that reclaim albumin via proximal tubular endocytosis.[35] Furthermore, Ware and colleges[11] described the renal cortical expression of the normally silent albumin gene that may exhibit characteristics of an acute tubular stress reactant, analogous to neutrophil-gelatinase lipocalin.

There are several aspects that are unique strengths of our study: (i) DA testing occurred at the time of AKI diagnosis in all participants; (ii) ascertainment of DA, specifically we analyzed DA in three ordinal categories (negative or trace, 30 mg/dL, and ≥100 mg/dL) and categorized a trace DA result as negative because of the possibility of a false positive result under the influence of high urinary concentration in the context of AKI; (iii) multivariable adjustment for appropriate confounders, including objective and comprehensive critical illness indicators; (iv) observation period up to 30 days following hospital discharge; and (v) inclusion of patients that died or were on RRT at the end of the observation period to avoid selection bias.

Our study also has limitations. First, the observational nature of our investigation could carry selection or misclassification bias. However, selection bias due to missing data is unlikely because data were not missing in a systematic differential manner in our cohort. Although our data are dependent on electronic medical record (EMR) documentation, the accuracy of data was validated by individual EMR review of 10% of data. Second, despite adjustment for confounding by rigorous multivariable regression analysis that included markers of severity of critical illness, residual confounding by unmeasured covariates may not have been completely eliminated. Third, urine output data for AKI adjudication or DA status adjustment were not available. The latter was offset in part by categorizing a trace DA result as negative because of the possibility of a false positive result under the influence of high urinary solute concentration in the context of oliguric AKI. Finally, SCr-based AKI recovery may not always be an accurate estimation of renal function recovery and not necessarily reflect histopathological recovery in every patient.

CONCLUSIONS

The presence of dipstick albuminuria ≥30 mg/dL is independently associated with lower rate of AKI recovery at 30 days following hospital discharge in ICU septic patients who suffered from AKI. We observed an indirect relationship between higher degree of DA and AKI recovery that may reflect more severe glomerular or tubular damage and less plausible AKI recovery with higher degree of DA. Our findings emphasize the importance and potential utility of a simple routine test of DA in the risk-stratification of AKI recovery in ICU septic patients.

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REFERENCES

1. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit. Care Med.* 2001; **29**: 1303–10.
2. Vincent JL, Sakr Y, Sprung CL *et al.* Sepsis in European intensive care units: results of the SOAP study. *Crit. Care Med.* 2006; **34**: 344–53.
3. Bagshaw SM, Uchino S, Bellomo R *et al.* Septic acute kidney injury in critically ill patients: clinical characteristics and outcomes. *Clin. J. Am. Soc. Nephrol.* 2007; **2**: 431–9.
4. Bagshaw SM, George C, Bellomo R. Early acute kidney injury and sepsis: a multicentre evaluation. *Crit. Care* 2008; **12**: R47. doi:10.1186/cc6863
5. Bagshaw SM, Lapinsky S, Dial S *et al.* Acute kidney injury in septic shock: clinical outcomes and impact of duration of hypotension prior to initiation of antimicrobial therapy. *Intensive Care Med.* 2009; **35**: 871–81.
6. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. *N. Engl. J. Med.* 2003; **348**: 138–50.
7. Aird WC. The role of the endothelium in severe sepsis and multiple organ dysfunction syndrome. *Blood* 2003; **101**: 3765–77.
8. Gosling P. Microalbuminuria: a marker of systemic disease. *Br. J. Hosp. Med.* 1995; **54**: 285–90.
9. Xu C, Chang A, Hack BK, Eadon MT, Alper SL, Cunningham PN. TNF-mediated damage to glomerular endothelium is an important determinant of acute kidney injury in sepsis. *Kidney Int.* 2014; **85**: 72–81.
10. Schreiber A, Theilig F, Schweda F, Hocherl K. Acute endotoxemia in mice induces downregulation of megalin and cubilin in the kidney. *Kidney Int.* 2012; **82**: 53–9.
11. Ware LB, Johnson AC, Zager RA. Renal cortical albumin gene induction and urinary albumin excretion in response to acute kidney injury. *Am. J. Physiol. Renal Physiol.* 2011; **300**: F628–38.
12. Clark JJ, Wong LL, Lurie F, Kamitaki BK. Proteinuria as a predictor of renal dysfunction in trauma patients receiving intravenous contrast. *Am. Surg.* 2011; **77**: 1194–200.
13. Molnar AO, Parikh CR, Sint K *et al.* Association of postoperative proteinuria with AKI after cardiac surgery among patients at high risk. *Clin. J. Am. Soc. Nephrol.* 2012; **7**: 1749–60.
14. Neyra JA, Manllo J, Li X, Jacobsen G, Yee J, Yessayan L. Association of de novo Dipstick Albuminuria with Severe Acute Kidney Injury in Critically Ill Septic Patients. *Nephron Clin. Pract.* 2015: 373–80.
15. Kellum JA, Lameire N. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). *Crit. Care* 2013; **17**: 204. doi:10.1186/cc11454

16. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann. Intern. Med.* 1999; **130**: 461–70.
17. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit. Care Med.* 1985; **13**: 818–29.
18. Vincent JL, Moreno R, Takala J *et al.* The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med.* 1996; **22**: 707–10.
19. Hobson CE, Yavas S, Segal MS *et al.* Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery. *Circulation* 2009; **119**: 2444–53.
20. Bihorac A, Yavas S, Subbiah S *et al.* Long-term risk of mortality and acute kidney injury during hospitalization after major surgery. *Ann. Surg.* 2009; **249**: 851–8.
21. Jones J, Holmen J, De Graauw J, Jovanovich A, Thornton S, Chonchol M. Association of complete recovery from acute kidney injury with incident CKD stage 3 and all-cause mortality. *Am. J. Kidney Dis.: Official J. National Kidney Foundation* 2012; **60**: 402–8.
22. Brown JR, Kramer RS, Coca SG, Parikh CR. Duration of acute kidney injury impacts long-term survival after cardiac surgery. *Ann. Thorac. Surg.* 2010; **90**: 1142–8.
23. Cerda J, Liu KD, Cruz DN *et al.* Promoting Kidney Function Recovery in Patients with AKI Requiring RRT. *Clin. J. Am. Soc. Nephrol.* 2015; **10**: 1859–67.
24. Sawhney S, Mitchell M, Marks A, Fluck N, Black C. Long-term prognosis after acute kidney injury (AKI): what is the role of baseline kidney function and recovery? A systematic review. *BMJ Open* 2015; **5** e006497.
25. Rewa O, Bagshaw SM. Acute kidney injury-epidemiology, outcomes and economics. *Nat. Rev. Nephrol.* 2014; **10**: 193–207.
26. Waikar SS, Liu KD, Chertow GM. Diagnosis, epidemiology and outcomes of acute kidney injury. *Clin. J. Am. Soc. Nephrol.* 2008; **3**: 844–61.
27. McCullough PA, Shaw AD, Haase M *et al.* Diagnosis of acute kidney injury using functional and injury biomarkers: workgroup statements from the tenth Acute Dialysis Quality Initiative Consensus Conference. *Contrib. Nephrol.* 2013; **182**: 13–29.
28. Perazella MA, Coca SG, Hall IE, Iyanam U, Koraishy M, Parikh CR. Urine microscopy is associated with severity and worsening of acute kidney injury in hospitalized patients. *Clin. J. Am. Soc. Nephrol.* 2010; **5**: 402–8.
29. Bagshaw SM, Haase M, Haase-Fielitz A, Bennett M, Devarajan P, Bellomo R. A prospective evaluation of urine microscopy in septic and non-septic acute kidney injury. *Nephrol. Dial. Transplant.: Official Publ. Eur. Dial. Transplant Assoc. – Eur. Renal Assoc.* 2012; **27**: 582–8.
30. Hu JY, Meng XC, Han J *et al.* Relation between proteinuria and acute kidney injury in patients with severe burns. *Crit. Care* 2012; **16**: R172. doi:10.1186/cc11649
31. Abid O, Sun Q, Sugimoto K, Mercan D, Vincent JL. Predictive value of microalbuminuria in medical ICU patients: results of a pilot study. *Chest* 2001; **120**: 1984–8.
32. Fleck A, Raines G, Hawker F *et al.* Increased vascular permeability: a major cause of hypoalbuminaemia in disease and injury. *Lancet* 1985; **1**: 781–4.
33. Jensen JS, Borch-Johnsen K, Jensen G, Feldt-Rasmussen B. Microalbuminuria reflects a generalized transvascular albumin leakiness in clinically healthy subjects. *Clin. Sci. (Lond.)* 1995; **88**: 629–33.
34. Kato T, Mizuno-Horikawa Y, Mizuno S. Decreases in podocin, CD2-associated protein (CD2AP) and tensin2 may be involved in albuminuria during septic acute renal failure. *J. Vet. Med. Sci.* 2011; **73**: 1579–84.
35. Dickson LE, Wagner MC, Sandoval RM, Molitoris BA. The proximal tubule and albuminuria: really!. *J. Am. Soc. Nephrol.: JASN* 2014; **25**: 443–53.