ORIGINAL ARTICLE

Admission hyperuricemia increases the risk of acute kidney injury in hospitalized patients[*]

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Abstract

Background: The association between elevated admission serum uric acid (SUA) and risk of in-hospital acute kidney injury (AKI) is limited. The aim of this study was to assess the risk of developing AKI in all hospitalized patients with various admission SUA levels.

Methods: This is a single-center retrospective study conducted at a tertiary referral hospital. All hospitalized adult patients who had admission SUA available from January 2011 through December 2013 were analyzed in this study. Admission SUA was categorized based on its distribution into six groups (<3.4, 3.4–4.5, 4.5–5.8, 5.8–7.6, 7.6–9.4 and >9.4 mg/dL). The primary outcome was in-hospital AKI occurring after hospital admission. Logistic regression analysis was performed to obtain the odds ratio (OR) of AKI of various admission SUA levels using the most common SUA level range (5.8–7.6 mg/dL) as the reference group.

Results: Of 1435 patients enrolled, AKI occurred in 263 patients (18%). The incidence of AKI and need for dialysis was increased in patients with higher admission SUA levels. After adjusting for potential confounders, SUA >9.4 mg/dL was associated with an increased risk of developing AKI, with ORs of 1.79 [95% confidence interval (CI) 1.13–2.82]. Conversely, admission SUA <3.4 and 3.4–4.5 mg/dL were associated with a decreased risk of developing AKI, with ORs of 0.38 (95% CI 0.17–0.75) and 0.50 (95% CI 0.28–0.87), respectively.

Conclusions: Elevated admission SUA was associated with an increased risk for in-hospital AKI.

Key words: acute kidney injury, hyperuricemia, length of hospital stay, mortality, uric acid

Introduction

Acute kidney injury (AKI) is a common clinical syndrome among hospitalized patients, independently associated with both short- and long-term mortality [1]. AKI-associated mortality has been reported to be as high as 23% [1]. Previous studies have attempted to identify effective interventions to prevent AKI events [2–4]. However, most were unsuccessful. Therefore further studies are needed to identify individuals who are at high risk of developing AKI.

Uric acid has been linked to AKI via crystal-independent mechanisms, including reduced renal blood flow and glomerular filtration rate (GFR), as well as crystal-dependent pathways [5]. Serum uric acid (SUA) measurement has been examined as a novel marker for early detection of AKI [6, 7]. Recent studies have demonstrated that an elevated SUA level is a risk factor for developing postoperative AKI in cardiovascular surgery patients [8–12]. However, the effect of admission SUA on the risk of in-hospital AKI in the general hospital population has not been examined. The objective of this study was to evaluate the risk of developing AKI in all hospitalized patients across a spectrum of SUA levels.

Materials and methods

Study population

The study included all adult (ages ≥18 years) patients admitted to the Mayo Clinic Rochester—a tertiary referral hospital—from 1 January 2011 through 31 December 2013. Exclusion criteria were patients without SUA measurement within 24 h of admission, patients with a history of end-stage renal disease (ESRD), patients who presented with AKI at the time of admission and patients who did not provide research authorization. Patients admitted after trauma were also not analyzed due to a higher incidence of bleeding and AKI at the time of admission [13]. For patients with multiple admissions during this period, only the first hospital admission was analyzed. ESRD was identified based on International Classification of Diseases, 9th revision (ICD-9 code assignment (Supplementary data, Table S1) or an estimated GFR (eGFR) <15 mL/min/1.73 m^2.

Data collection

Clinical characteristics, demographic information and laboratory data were collected using manual and automated retrieval from the institutional electronic medical record system. The admission SUA level, defined as the first SUA level within 24 h of hospital admission, was collected. eGFR was derived using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [14]. Chronic kidney disease (CKD) was defined as a calculated eGFR <60 mL/min/1.73 m^2. The Charlson comorbidity score [15] was computed for comorbidities at the time of admission. Principal diagnoses were grouped based on ICD-9 codes at admission (Supplementary data, Table S2).

Clinical outcomes

The primary outcome was AKI, based on the serum creatinine (SCr) criterion of the Kidney Disease Improving Global Outcomes (KDIGO) definition (Supplementary data, Table S3) [16]. AKI was defined as an increase in SCr ≥0.3 mg/dL within 48 h or ≥1.5 times baseline within 7 days after admission date. The baseline SCr was defined as the minimum SCr measured within 1 year before admission. If outpatient SCr was not available, the Modification of Diet in Renal Disease equation [17] was used to estimate the baseline SCr level, assuming normal baseline GFR of 75 mL/min/1.73 m^2, in accordance with this guideline [16]. We performed sensitivity analysis using any in-hospital AKI occurrence, regardless of 7-day the time frame. Secondary outcomes were in-hospital mortality, 90-day mortality after hospital admission, hospital length of stay (LOS) and discharge to a care facility. In patients whose vital status at 90 days after hospital admission based on the institutional electronic medical record was unknown, the Social Security Death Index was used [18].

Statistical analysis

Continuous variables are reported as mean ± SD for normally distributed data and median (IQR) for non-normally distributed data. All categorical variables are reported as count with percentage. Baseline demographics and clinical characteristics were compared among the admission uric acid group, using analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical variables. We categorized admission serum uric levels, based on six-quantile percentiles (10% | 25% | 50% | 75% | 90%): <3.4, 3.4–4.5, 4.5–5.8, 5.8–7.6, 7.6–9.4 and >9.4 mg/dL. The most common SUA level range (5.8–7.6 mg/dL) was selected as the reference group for outcome comparison (Table 1). We performed univariate analysis and then multivariate logistic regression analysis to evaluate the independent association between admission uric acid levels and AKI. Odds ratios (ORs) with 95% confidence intervals (CIs) are reported. The OR was adjusted for variables with statistically significant (P-value <0.05) differences between groups in univariate analysis. The adjusting variables were age, sex, body mass index (BMI), baseline SCr, principal diagnosis comorbidities and medications. Comorbidities were coronary artery disease (CAD), hypertension (HTN), diabetes mellitus (DM) and congestive heart failure (CHF). Medications were angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs) and diuretics. A two-tailed P-value <0.05 was considered statistically significant. All analyses were performed using JMP statistical software (version 10, SAS Institute, Cary, NC, USA).

Results

A total of 76 719 adult patients were identified. After excluding 73 295 patients who lacked admission uric acid measurement, 390 patients with ESRD, 762 patients with AKI at presentation and 837 trauma patients, 1435 unique patients were enrolled (Supplementary data, Figure S1).

Baseline characteristics

Of 1435 patients, 865 (91.4%) patients were Caucasian and 865 (60.3%) were male (Table 1). The mean age was 62 ± 16 years. Patient age was positively correlated with SUA, whereas eGFR was inversely correlated with SUA. Patient comorbidities included HTN (48.7%), DM (22.1%), CAD (19.0%) and CHF (12.8%). Forty-nine per cent of the patients were taking diuretics, 37.3% were taking ACEIs or ARBs and 15.3% were taking allopurinol before admission. The distribution of admission serum uric levels was normally distributed (Supplementary data, Figure S2).

The principle admission diagnosis showed that patients with a diagnosis of cardiovascular diseases presented with high admission SUA, whereas patients with diagnoses of hematology/oncology, infectious, endocrine/metabolic and respiratory diseases presented with low admission SUA (Supplementary data, Figure S3).

Admission SUA and the incidence of AKI

The incidence of AKI associated with admission SUA was linear (Figure 1). The lowest AKI incidence occurred when SUA levels were <3.4 mg/dL. Increasing SUA levels were correlated with higher incidences of all stages of AKI. Increasing SUA levels were also positively correlated with the need for dialysis, with the highest incidence in patients with SUA >9.4 mg/dL (Table 2). Despite minimal mortality, there was a trend of higher mortality with increasing admission SUA, with the highest mortality when

Table 1. Baseline clinical characteristics

Variables	All	SUA level at hospital admission (mg/dL)						P-value
		<3.4	3.4–4.5	4.5–5.8	5.8–7.6	7.6–9.4	>9.4	
Patients (n)	1435	135	223	337	374	216	150	
Age (years)	62.0 ± 16.0	58.3 ± 17.4	59.7 ± 17.3	60.9 ± 15.9	63.0 ± 15.8	64.8 ± 14.1	64.4 ± 15.3	<0.001
Male	865 (60.3%)	64 (47.4%)	99 (44.4%)	197 (58.5%)	253 (67.6%)	149 (70.0%)	103 (68.7%)	<0.001
Caucasian	1311 (91.4%)	126 (93.3%)	207 (92.8%)	303 (89.9%)	347 (92.8%)	195 (90.3%)	133 (88.7%)	0.44
BMI (kg/m^2)	29.1 ± 7.3	26.6 ± 6.0	26.3 ± 6.8	28.2 ± 7.0	30.3 ± 6.8	30.5 ± 7.1	32.5 ± 8.4	<0.001
Weight change in hospital (kg)	−0.9 ± 6.0	−0.5 ± 4.8	−0.8 ± 4.7	−0.5 ± 6.0	−0.9 ± 6.6	−1.3 ± 6.1	−2.1 ± 7.2	0.14
Charlson comorbidity score	2.0 ± 2.4	1.7 ± 2.3	2.2 ± 2.6	1.9 ± 2.3	2.0 ± 2.3	2.2 ± 2.4	2.0 ± 2.2	0.33
Baseline serum creatinine (mg/dL)	1.1 ± 0.4	0.9 ± 0.2	0.9 ± 0.2	1.0 ± 0.3	1.1 ± 0.3	1.2 ± 0.5	1.3 ± 0.5	<0.001
eGFR (mL/min/1.73 m^2)	73.1 ± 26.1	89.5 ± 20.6	88.1 ± 21.9	79.3 ± 24.5	71.7 ± 24.8	58.6 ± 22.3	53.2 ± 21.8	<0.001
Comorbidities								
CAD	273 (19.0%)	18 (13.3%)	21 (9.4%)	54 (16.0%)	78 (20.9%)	53 (24.5%)	49 (32.7%)	<0.001
HTN	699 (48.7%)	55 (40.7%)	83 (37.2%)	140 (41.5%)	214 (57.2%)	125 (57.9%)	82 (54.7%)	<0.001
DM	317 (22.1%)	15 (13.3%)	49 (22.0%)	63 (18.7%)	83 (22.2%)	63 (29.2%)	41 (27.3%)	0.005
CHF	184 (12.8%)	8 (5.9%)	13 (5.8%)	28 (8.3%)	45 (12.0%)	40 (18.5%)	50 (33.3%)	<0.001
Cirrhosis	60 (4.2%)	5 (3.7%)	12 (5.4%)	12 (3.6%)	14 (3.7%)	11 (5.1%)	6 (4.0%)	0.87
Principal diagnosis								<0.001
Cardiovascular	487 (33.9%)	15 (11.1%)	38 (17.0%)	101 (30.0%)	145 (38.8%)	103 (47.7%)	85 (56.7%)	
Hematology/oncology	378 (26.3%)	57 (42.2%)	74 (33.2%)	92 (27.3%)	88 (23.5%)	45 (20.8%)	22 (14.7%)	
Infectious disease	53 (3.7%)	12 (8.9%)	9 (4.0%)	13 (3.9%)	9 (2.4%)	6 (2.8%)	4 (2.7%)	
Endocrine/metabolic	94 (6.6%)	14 (10.4%)	14 (6.3%)	18 (5.3%)	23 (6.2%)	14 (6.5%)	11 (7.3%)	
Respiratory	59 (4.1%)	8 (6.0%)	13 (5.8%)	19 (5.6%)	12 (3.2%)	3 (1.4%)	4 (2.7%)	
Gastrointestinal	74 (5.1%)	10 (7.4%)	14 (6.3%)	19 (5.6%)	20 (5.3%)	11 (5.1%)	4 (2.7%)	
Other	290 (20.2%)	19 (14.1%)	61 (27.4%)	79 (23.4%)	77 (20.6%)	34 (15.7%)	20 (13.3%)	
Medication								
ACEI/ARB	535 (37.3%)	32 (23.7%)	49 (22.0%)	109 (32.3%)	163 (43.6%)	95 (44.0%)	87 (58%)	<0.001
NSAID	235 (16.4%)	23 (17.0%)	46 (20.6%)	65 (19.3%)	58 (15.5%)	26 (12.0%)	17 (11.3%)	0.05
Diuretic	703 (49.0%)	37 (27.4%)	60 (26.9%)	134 (39.8%)	206 (55.1%)	139 (64.4%)	127 (84.7%)	<0.001
Allopurinol	219 (15.3%)	21 (15.6%)	26 (11.7%)	49 (14.5%)	58 (15.5%)	35 (16.2%)	30 (20%)	0.40
Shock	153 (10.7%)	8 (5.9%)	19 (8.5%)	40 (11.9%)	40 (10.7%)	25 (11.6%)	21 (14.0%)	0.24

Continuous data are presented as mean ± SD; categorical data are presented as n (%).
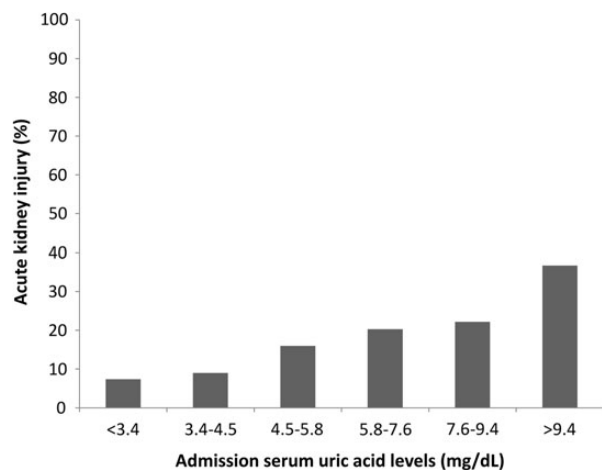

Fig. 1. In-hospital AKI within 7 days for various admission SUA levels.

SUA was >9.4 mg/dL. Both low admission SUA (<3.4 mg/dL) and high SUA (>9.4 mg/dL) were correlated with longer hospital LOS, whereas patients with admission SUA >9.4 mg/dL had the highest rate of discharge to a care facility.

Admission SUA and risk of AKI

To assess whether admission SUA levels contributed to AKI development, logistic regression models were built, using 5.8–7.6 mg/dL as a reference range. An unadjusted admission SUA >9.4 mg/dL was associated with an increased risk of AKI [OR 2.27 (95% CI 1.50–3.44)] (Table 3). Conversely, SUA <3.4 mg/dL was associated with a reduced risk of AKI [OR 0.31 (95% CI 0.15–0.60)]. An admission SUA of 3.4–4.5 mg/dL was associated with a reduced risk of AKI [OR 0.39 (95% CI 0.22–0.64)]. When adjusted for all variables including age, sex, BMI, baseline SCr, comorbidities and medications, these associations remained statistically significant. High admission SUA (>9.4 mg/dL) was associated with an increased risk of developing AKI [OR 1.79 (95% CI 1.79–2.82)] (Table 3). An SUA <3.4 mg/dL was associated with a decreased AKI [OR 0.38 (95% CI 0.17–0.75)] and an admission SUA of 3.4–4.5 mg/dL was associated with decreased AKI [OR 0.50 (95% CI 0.28–0.87)].

Sensitivity analysis

These findings remained when AKI outcome was reanalyzed without the limitation of 7 days after admission (Supplementary data, Tables S4 and S5). The linear trend of higher in-hospital AKI with increasing SUA still existed, with the highest incidence in patients with admission SUA >9.4 mg/dL (Supplementary data, Table S4) with increased in-hospital AKI [OR 1.89 (95% CI 1.21–2.95)] (Supplementary data, Table S5).

Discussion

This study demonstrates that the admission SUA level is correlated with the incidence of AKI and the need for dialysis during

Table 2. Outcomes

Outcome	SUA level at hospital admission (mg/dL)						P-value
	<3.4	3.4–4.5	4.5–5.8	5.8–7.6	7.6–9.4	>9.4	
AKI	10 (7.4%)	20 (9.0%)	54 (16.0%)	76 (20.3%)	48 (22.2%)	55 (36.7%)	<0.001
AKI stage							<0.001
Stage 1	7 (5.2%)	18 (8.1%)	44 (13.1%)	57 (15.2%)	41 (19.0%)	43 (28.7%)	
Stage 2	3 (2.2%)	2 (0.9%)	7 (2.1%)	9 (2.4%)	3 (1.4%)	5 (3.3%)	
Stage 3	0 (0%)	0 (0)	3 (0.9%)	10 (2.7%)	4 (1.9%)	7 (4.7%)	
Dialysis	0 (0%)	0 (0%)	7 (2.1%)	7 (1.9%)	3 (1.4%)	6 (4.0%)	0.03
In-hospital mortality	3 (2.2%)	4 (1.8%)	8 (2.4%)	8 (2.1%)	4 (1.9%)	4 (2.7%)	0.99
90-day mortality	25 (18.5%)	29 (13.0%)	42 (12.5%)	38 (10.2%)	21 (9.7%)	16 (10.7%)	0.14
Hospital LOS (days), mean (range)	7 (4–14)	5 (3–10)	5 (4–10)	5 (3–8)	6 (3–10)	6.5 (4–11)	0.03
Discharge to care facility[a]	7 (7.9%)	14 (8.3%)	14 (5.5%)	13 (4.6%)	13 (7.9%)	9 (9.3%)	0.42

Values are given as n (%).
[a]Denominator was hospital survivors.

Table 3. Odds ratios for association between admission SUA levels and in-hospital AKI occurrence within 7 days

SUA level at hospital admission (mg/dL)	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	Adjusted[a] OR (95% CI)	P-value
<3.4	0.31 (0.15–0.60)	0.001	0.38 (0.17–0.75)	0.005
3.4–4.5	0.39 (0.22–0.64)	<0.001	0.50 (0.28–0.87)	0.01
4.5–5.8	0.75 (0.51–1.10)	0.14	0.86 (0.57–1.28)	0.45
5.8–7.6	1 (ref)		1 (ref)	
7.6–9.4	1.12 (0.74–1.68)	0.59	1.03 (0.67–1.58)	0.89
>9.4	2.27 (1.50–3.44)	<0.001	1.79 (1.13–2.82)	0.01

[a]Adjusted for age, gender, BMI, baseline SCr, comorbidities (including CAD, hypertension, diabetes, CHF), principal diagnosis and medication use (including angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers and diuretics).

hospitalization. This correlation occurs at all stages of AKI. There is also a positive correlation between admission SUA level and the risk of developing AKI, with the highest risk in the admission SUA >9.4 mg/dL patient group. The lowest risk group was admission SUA <3.4 mg/dL.

There are several plausible explanations for the increased AKI risk in patients with elevated SUA values. Uric acid has been proposed to play a role in AKI via crystal-independent mechanisms, as well as crystal-dependent pathways [5]. Elevated SUA can induce renal vasoconstriction and impair autoregulation, which results in reduced renal blood flow and GFR [5, 8, 19]. Sanchez-Lozada *et al.* [20] showed that even a mild elevation of SUA can cause renal vasoconstriction in rats without evidence of intratubular crystal precipitation. Furthermore, hyperuricemia has been shown to worsen renal injury via pro-inflammatory pathways involving chemokine expression with leukocyte infiltration, as well as proliferation of vascular smooth muscle cells and inhibition of endothelial function [8, 21–23]. AKI-related crystal-dependent pathways can also occur in renal stones and acute urate nephropathy associated with tumor lysis syndrome [19, 24–27].

Previous reports have demonstrated that elevated SUA is a risk factor for developing AKI in specific circumstances. Preoperative and postoperative hyperuricemia has been linked to a higher incidence of postoperative AKI, especially in cardiovascular surgery settings [8–12]. Moreover, hyperuricemia has also been shown to increase the risk of contrast-induced AKI after percutaneous coronary interventions [28, 29]. Hyperuricemia at baseline has also been shown to be an important long-term predictor of AKI and mortality [30], especially in the elderly with CKD [31]. In cases of acute paraquat intoxication, baseline

SUA has been proposed as a clinical marker of AKI and mortality [32]. Ongoing research to identify novel biomarkers for AKI diagnosis and risk stratification has the potential to reduce delays in the diagnosis of AKI in the hospital setting [33]. SUA measurement has been proposed as a novel marker for early detection of AKI [6, 7]. The results presented in our study are the first to demonstrate that SUA at the time of admission is an important predictor of developing in-hospital AKI in the general hospitalized patient.

Recently Lapsia *et al.* [8] demonstrated a J-shaped relationship between preoperative SUA and postoperative AKI. The proposed explanation was that AKI-associated hypouricemia is due to oxidative stress, as uric acid can act as both an antioxidant and pro-oxidant agent, depending on the SUA level [21, 34, 35]. However, the results of our study of hospitalized patients reveal a positive linear correlation between admission SUA level and the risk of developing AKI. This difference may be due to different study populations and settings.

The results of our study demonstrate a prognostic effect of admission SUA level on AKI development. Previous attempts to identify effective interventions to prevent AKI have been largely unsuccessful [2, 3]. Using the admission SUA level in clinical practice may help identify patients with a high risk of AKI during hospitalization in order to promptly prevent AKI events. For example, hyperuricemia-related AKI has been reported in patients with non-steroidal anti-inflammatory drug use. Thus discontinuation or avoidance of such nephrotoxic agents in patients with elevated admission SUA should be considered. Several clinical trials have examined the efficacy of uric acid–lowering agents, such as allopurinol, in cardiovascular surgery and found a reduction in the production of reactive oxygen species [36, 37].

Recently, long-term follow-up of a randomized clinical trial showed that long-term treatment with allopurinol may slow the rate of progression of kidney disease and decrease cardiovascular risks [38]. Rasburicase has also been studied in a prospective, double-blind, placebo-controlled, randomized trial of 26 hyperuricemic patients undergoing cardiac surgery [39]. Despite no observed benefit on postoperative SCr, markers of structural renal injury such as urine neutrophil-associated lipocalin (uNGAL) tended to be lower in rasburicase-treated patients.

This study has several limitations. First, this is a single-center, retrospective study. Second, the patient population in this study is relatively homogeneous (predominantly Caucasian). Further studies with a more heterogeneous population are desirable to ascertain the clinical effects of admission SUA on AKI in a broad patient population. A multicenter, prospective study is ultimately required to address these limitations. (3) Our study demonstrated that the lowest SUA level group (<3.4 mg/dL) was correlated with the longest hospital LOS. Principal diagnoses likely played important roles for this association since those patients had more diagnoses of hematology/oncology or infectious diseases, as indicated in Table 1. Malnutrition and inflammation were suggested to be important factors for lower SUA levels and worse outcome. However, the data regarding C-reactive protein and albumin were limited since they were not commonly measured in hospitalized patients. Finally, there is potential selection bias, as those patients who had admission SUA measurements may have had different clinical characteristics from others who did not have admission SUA measurements. A multicenter, prospective study is ultimately required to address these limitations.

In conclusion, this study demonstrates that elevated admission SUA is associated with an increased risk for in-hospital AKI.

Authors' contributions

All the authors had access to the data and a role in writing the manuscript.

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Supplementary data

Supplementary data are available online at http://ndt.oxfordjournals.org.

Conflict of interest statement

None declared.

(See related article by Kaushik and Choo. Serum uric acid and AKI: is it time? Clin Kidney J (2016) 9: 48–50.)

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