e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2023; 15(12); 705-710

Original Research Article

Study of Serum Uric Acid Levels with the Severity of Kidney Injury in COVID Disease

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Received: 12-10-2023 Revised: 15-11-2023 / Accepted: 24-12-2023
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Conflict of interest: Nil

Abstract

Aim: The aim of the present study was to assess the Serum uric acid levels with the severity of acute kidney injury.

Methods: This study enrolled patients who developed AKI within 48 h of hospitalization at the Government Institute of Medical Sciences (GIMS), Greater Noida from March 2020 and February 2021. According to the inclusion and exclusion criteria, 1200 patients with AKI within 48 h after hospital admission were included.

Results: Among all patients, the mean age was 58.1 years, and 640 (53.34%) were men. Compared with the lowest SUA group (≤3.6 mg/dL), the highest SUA group (>6.9 mg/dL) had a higher proportion of patients with CKD and hypertension. Regarding laboratory parameters, patients with higher SUA levels also had higher BMI, creatinine and triglyceride values Moreover, they were more likely to require RRT than patients with lower SUA (≤3.6 mg/dL). In multivariable analysis of model 1, which was adjusted for age, sex and BMI, the ORs were 1.46 (95% CI, 1.01–2.12) in the SUA level >5.0–6.9 mg/dl group and 3.16 (95% CI, 2.25–4.45) in the SUA level >6.9 mg/dl group compared with the reference group (SUA ≤3.6 mg/dl). After adjustment for age; sex; BMI; emergency status; AKI stage; the presence of CKD, diabetes, hypertension, heart disease, or cancer; creatinine; albumin; cholesterol; tri- glyceride; Hb; eGFR; RRT requirement; and the use of ACEIs, ARBs, beta blockers, CCBs, furosemide and UA- lowering agents, a similar trend was observed in analysis of model 2. A higher SUA level was associated with an increased risk of in-hospital mortality in AKI patients.

Conclusion: We found that the SUA concentration appeared to be an independent prognostic marker of in-hospital mortality in AKI patients within 48 h after hospital admission and that elevated SUA levels were associated with an increased risk of in-hospital mortality and rate of non-recovery of renal function in these patients.

Keywords: Acute kidney injury; serum uric acid; mortality; prognostic

Introduction

Acute kidney injury (AKI) is a common and severe syndrome associated with high morbidity and mortality. [1] AKI occurs in 21% of hospitalized patients and sometimes in more than 50% of patients

in intensive care units; the mortality rate of AKI patients is four times higher than that of non-AKI patients. [2] It is therefore important to understand if high uric acid levels modify kidney or metabolic outcomes. This is especially true because hyperuricemia is an independent predictor of CKD and metabolic diseases, [3–5] including in subjects who are healthy without any morbidities. [6] There is also a direct relationship of serum uric acid level with prevalence of hypertension, diabetes, and CKD. [7,8]

The definition of hyperuricemia differs between males and females. Females usually have lower serum uric acid (UA) levels than men. Male sex is a significant risk factor for hyperuricemia and gout; males have been affected four-fold more frequently than females. [9-12] Hyperuricemia predicts mortality from heart failure, cerebrovascular and cardiac ischemic events, hypertension, and metabolic syndrome. An elevated serum UA level has been shown to be an independent risk factor for chronic kidney disease and renal function failure. [13-15]

Hyperuricemia is very prevalent among chronic kidney disease (CKD) patients because of the decrease in renal excretion of UA when the eGFR declines. In addition, studies have demonstrated that hyperuricemia is a risk factor for all-cause mortality and cardiovascular events in the earlier stages of CKD but not renal replacement therapy. [16,17] The association between SUA levels and mortality has been inconsistent among studies of patients with end-stage renal disease who are receiving hemodialysis and peritoneal dialysis. Interestingly, in most studies involving patients receiving hemodialysis, elevated SUA levels were associated with lower mortality, which is called an 'inverse epidemiological phenomenon'. [18]

The aim of the present study was to assess the Serum uric acid levels with the severity of acute kidney injury.

Materials and Methods

This study enrolled patients who developed AKI within 48 h of hospitalization at the Government Institute of Medical Sciences, Greater Noida from March 2020 to February 2021. According to the inclusion and exclusion criteria, 1200 patients with AKI within 48 h after hospital admission were included. AKI patients were identified according to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 criteria, which are as follows: (1) an increase in serum creatinine to more than 1.5-fold the baseline values ; (2) a $\geq$ 0.3 mg/dl increase in serum creatinine or (3) urine out- put <0.5 mL/kg/h for 6 h or more. We excluded the urine output criteria because most inpatients lacked urine volume records.

Patients were excluded if they met one of the following characteristics: (1) younger than 18 years; (2) hospitalization for <24 h; or (3) fewer than two serum creatinine tests.

After excluding patients with less than two serum creatinine tests, the average number of serum creatinine tests for all patients was 3, and 58.8% of patients had 2 serum creatinine tests. For patients who were admitted to the hospital more than once, only the first stay was included.

Data Extraction

Data extracted from the electronic medical records included age, sex, body mass index (BMI), emergency status, AKI stage, and the presence of CKD, diabetes, hypertension, heart disease and cancer. Blood laboratory data, including SUA, creatinine, albumin (ALB), cholesterol, triglyceride and hemoglobin (Hb), were measured at the time of admission. Medications such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta receptor blockers, calcium channel blockers (CCBs), furosemide and UA-lowering agents were investigated. All biochemical indexes value on the first day after admission was included. Hyperuricemia was defined as fasting blood uric acid levels higher than 7.0 mg/dl on two different days with a normal purine diet. BMI was calculated as body weight divided by height squared (kg/m2). UA-lowering agent use was defined as the use of any UA-lowering agent, including febuxostat, allopurinol, and benzbromarone, after admission.

Statistical Analysis:

Categorical variables were described as numbers (%). Continuous variables were analyzed parametrically by means and standard deviations and non parametrically by median, minimum and maximum. Differences between categorical variables were calculated using the chi-square method. A P-value less than 0.05 were considered statistically significant. Statistical analyses were performed using SPSS software (version 17.0).

Results

Table 1: Baseline characteristics

Parameters	Uric acid				P Value
	≤3.6 (N=300)	>3.6–5.1 (N=300)	>5.1–6.9 (N=300)	>6.9 (N=300)	
Age	56.8 ± 17.8	56.9 ± 18.7	59.0 ± 17.7	59.5 ± 17.9	0.450
Sex, male, n (%)	120 (40)	150 (50)	175 (58.34)	195 (65)	<0.001
BMI (kg/m2)	23.6 ± 3.4	24.4 ± 3.7	24.8 ± 3.9	25.1 ± 4.3	0.956
Emergency status, n (%)	160 (53.34)	148 (49.34)	125 (41.66)	122 (40.66)	0.888
AKI stage, n (%)					<0.001
Stage I	260 (86.66)	264 (88)	270 (90)	272 (90.66)	
Stage II	30 (10)	28 (9.34)	15 (5)	10 (3.34)	
Stage III	10 (3.34)	8 (2.66)	15 (5)	18 (6)	
Comorbidities, n (%)					
CKD	15 (5)	12 (4)	60 (20)	95 (31.66)	0.879
Diabetes	60 (20)	75 (25)	80 (28.34)	75 (25)	0.974
Hypertension	90 (30)	135 (45)	180 (60)	195 (65)	0.890
Heart disease	45 (15)	75 (25)	100 (33.34)	95 (31.66)	0.782
Biochemical indices					
Creatinine (mol/L)	1.14 ± 0.92	0.98 ± 0.83	1.30 ± 0.99	1.28 ± 0.70	0.560
Albumin (g/L)	4.01 ± 0.58	3.98 ± 0.53	4.04 ± 0.63	4.08 ± 0.72	0.645
Total Cholesterol (g/L)	186.25 ± 49.8	192.09 ± 53.42	180.20 ± 45.12	184.16 ± 1.44	0.723
Triglyceride (g/L)	153.95 ± 123.71	135.04 ± 92.71	173.54 ± 146.84	175.12 ± 80.20	0.859
Hb (g/L)	10.2 ± 0.13	10.8 ± 0.12	11 ± 0.20	11.5 ± 0.25	0.901
Medication					
ACEI (%)	6 (2)	12 (4)	18 (6)	22 (7.34)	0.890
ARB (%)	30 (10)	60 (20)	85 (28.34)	75 (25)	0.309
BB (%)	110 (36.66)	135 (45)	165 (55)	170 (56.6)	0.412
CCB (%)	60 (20)	84 (28)	112 (37.34)	125 (41.66)	0.429
Furosemide (%)	45 (16)	60 (20)	75 (25)	105 (35)	0.502
UA-lowering agent (%)	2 (0.6)	3 (1)	5 (1.6)	24 (8)	0.409
eGFR, ml/min/1.73 m2	75.8 ± 25.5	61.3 ± 29.0	48.1 ± 28.2	29.8 ± 24.3	0.986
RRT requirement	21 (7)	32 (10.6)	45 (15)	75 (25)	0.601

Among all patients, the mean age was 58.1 years, and 640 (53.34%) were men. Compared with the lowest SUA group (≤3.6 mg/dL), the highest SUA group (>6.9 mg/dL) had a higher proportion of patients with CKD and hypertension. Regarding laboratory parameters, patients with higher SUA levels also had higher BMI, creatinine and triglyceride values. Moreover, they were more likely to require RRT than patients with lower SUA (≤3.6 mg/dL).

Table 2: Odds ratio for in-hospital mortality according to SUA levels

		Unadjusted			Model 1			Model 2		
SUA (mg/dl)	OR	95% CI	*p* Value	OR	95% CI	*p* Value	OR	95% CI	*p* Value	
≤3.6	reference			reference			reference			
>3.6–5.1	1.37	0.94–2.01	0.098	1.31	0.89–1.92	0.172	1.24	0.82–1.88	0.306	
>5.1–6.9	1.67	1.16–2.39	0.006	1.46	1.01–2.12	0.044	1.72	1.21–2.33	0.005	
>6.9	3.64	2.62–5.05	<0.001	3.16	2.25–4.45	<0.001	2.75	1.78–4.26	<0.001	

In multivariable analysis of model 1, which was adjusted for age, sex and BMI, the ORs were 1.46 (95% CI, 1.01–2.12) in the SUA level >5.0–6.9 mg/dl group and 3.16 (95% CI, 2.25–4.45) in the SUA level >6.9 mg/dl group compared with the reference group (SUA ≤3.6 mg/dl). After adjustment for age; sex; BMI; emergency status; AKI stage; the presence of CKD, diabetes, hypertension, heart disease, or cancer; creatinine; alb; cholesterol; triglyceride; Hb; eGFR; RRT requirement; and the use of ACEIs, ARBs, beta blockers, CCBs, furosemide and UA- lowering agents, a similar trend was observed in analysis of model 2. A higher SUA level was associated with an increased risk of in-hospital mortality in AKI patients.

Table 3: Odds ratio for nonrecovery of AKI according to SUA levels

		Unadjusted			Model 1			Model 2	
SUA (mg/dl)	OR	95% CI	*p* Value	OR	95% CI	*p* Value	OR	95% CI	*p* Value
≤3.6	reference			reference			reference		
>3.6–5.1	1.03	0.88–1.22	0.671	1.09	0.92–1.290.340		1.14	0.86–1.520.167	
>5.1–6.9	1.15	0.88–1.33	0.120	1.12	0.79–1.300.428		1.07	0.92–1.200.258	
>6.9	1.51	1.12–2.01	0.012	1.59	1.07–1.98 <0.001		1.46	1.25–1.85 <0.001	

In the multivariable analysis of model 1, after adjustment for age, sex and BMI, the OR for AKI patients with SUA levels >6.9 mg/dl whose renal function had not recovered was higher than that in those with SUA levels ≤3.6 mg/dl (OR, 1.59, 95% CI, 1.07–1.98, p < 0.001). A similar trend was observed for model 2 after adjustment for various confounding factors (SUA levels >6.9 mg/dl versus ≤3.6 mg/dl: OR, 1.46, 95% CI, 1.25–1.85, p < 0.001).

Table 4: Performance of SUA levels for predicting in-hospital mortality in patients with AKI

Variables	AUC (95% CI)	Sensitivity	Specificity	*p* Value
SUA	0.65 (0.62–0.68)	0.51	0.73	<0.001
Age+ SUA	0.74 (0.71–0.77)	0.64	0.74	<0.001

When SUA level was combined with age to predict in-hospital mortality in AKI patients, the AUC reached the maximum value of 0.74; in addition, the sensitivity and specificity increased to 0.64 and 0.74 respectively.

Discussion

Acute kidney injury (AKI) is a common and severe syndrome associated with high morbidity and mortality. [19] AKI occurs in 21% of hospitalized patients and some- times in more than 50% of patients in intensive care units; the mortality rate of AKI patients is four times higher than that of non-AKI patients. [20-22] In addition, survivors often fail to recover renal function and require long-term dialysis, which imposes a significant financial burden. [23-25] Recognition of the clinical features that have the greatest impact on mortality in patients with AKI can help to guide supportive care for those most likely to benefit. Considering the high incidence and poor prognosis of AKI, several researchers have sought to identify risk factors for mortality in AKI. Among all patients, the mean age was 58.1 years, and 640 (53.34%) were men. Compared with the lowest SUA group (≤3.6 mg/dL), the highest SUA group (>6.9 mg/dL) had a higher proportion of patients with CKD and hypertension. Regarding laboratory parameters, patients with higher SUA levels also had higher BMI, creatinine and triglyceride values. Moreover, they were more likely to require RRT than patients with lower SUA (≤3.6 mg/dL).

A higher SUA level was associated with an increased risk of in-hospital mortality in AKI patients. A similar trend was observed for model 2 after adjustment for various confounding factors (SUA levels >6.9 mg/dl versus ≤3.6 mg/dl: OR, 1.46, 95% CI, 1.25–1.85, p < 0.001). AKI is the most common life-threatening complication in hospitalized patients and has a high mortality rate. [26] Previous studies have demonstrated that systemic and local inflammation are closely associated with the occurrence and development of AKI. [27] Several studies have been proposed to investigate the mechanisms underlying the systemic inflammatory response in patients with AKI. Moreover, iron metabolism and bone marrow function may be inhibited by the systemic inflammatory response. [28] The release of proinflammatory cytokines inhibits erythrocyte maturation and proliferation. [29] In addition, the

degree of inflammation has a considerably negative impact on patient survival. [30] Many studies have confirmed a certain correlation between high SUA levels and the inflammatory response, oxidative stress and activation of the renin-angiotensin system. [31]

SUA levels are associated with glomerular filtration and tubule reabsorption. Causes of high SUA levels may include reduced eGFR, decreased renal tubule UA secretion, enhanced renal tubule reabsorption capacity, or excessive UA production caused by metabolic diseases. [32] AKI is usually accompanied by a decrease in eGFR or injury of the renal tubules and renal interstitium, which may be associated with an increase in SUA levels in AKI patients. A prospective clinical study confirmed that among patients with hyperuricemia undergoing high-risk heart surgery, the uric acid oxidase-treated group should have less renal structural damage than the placebo- treated group. [33] Another study confirmed that UA oxidase application decreased the level of serum uric acid and increased the mean eGFR from 55 mL / min/1.73 m2 to 136 mL/min/1.73 m^2 in the treatment of tumor lysis syndrome in children with advanced mature B-cell non-Hodgkin lymphoma. [34] When SUA level was combined with age to predict in-hospital mortality in AKI patients, the AUC reached the maximum value of 0.74; in addition, the sensitivity and specificity increased to 0.64 and 0.74 respectively.

Conclusion

We found that the SUA concentration when combined with age has maximum AUC of 0.74 with sensitivity and specificity of (0.64 and 0.74) appeared to be an independent prognostic marker of in-hospital mortality in AKI patients within 48 h after hospital admission and that elevated SUA levels were associated with an increased risk of in-hospital mortality and rate of nonrecovery of renal function in these patients.

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