Disease and Diagnosis

→ **Original Article**

Could Basal Uric Acid Levels Be an Important Biomarker for Prediction of Acute Renal Injury in Patients With Sepsis in the Intensive Care Unit?

Harun Düğeroğlu[1]* , Murat Özgenoğlu[2]

[1]Department of Internal Medicine, Ordu University Faculty of Medicine, Ordu, Turkey.
[2]Edremit State Hospital, Clinic of Internal Medicine, Balıkesir, Turkey.

Abstract

Background: Sepsis is an important risk factor for the development of acute renal injury (ARI) among patients admitted to the intensive care unit (ICU). There are limited studies showing that increased uric acid level is an important risk factor for the development of ARI. The present study was carried out to find out whether increased basal uric acid levels play an important role in predicting the development of ARI and whether it could be used as a biomarker for this.

Materials and Methods: This retrospective study included patients aged ≥ 18 years who were admitted to the ICU of Yüzüncü Yıl University Medical Faculty Hospital from September 2018 to December 2020. Group 1 comprised 100 patients developing ARI and group 2 comprised 110 patients who did not develop ARI. Laboratory test values and Simplified Acute Physiologic Score II (SAPS II) data on the first day of ICU admission were obtained from archive records.

Results: During the 10-day follow-up of patients included in the study, the ARI development rate was 57.3%. Basal serum uric acid levels were higher in group 1 compared to group 2 ($P=0.001$). Based on the results of the multivariate logistic regression analysis, basal serum uric acid values and albumin and SAPS II values had independent correlations with ARI ($P<0.001$).

Conclusion: We believe that increased basal uric acid levels examined in patients admitted to the ICU with sepsis diagnosis may be an important biomarker for the prediction of ARI.

Keywords: Uric acid, Acute renal injury, Sepsis, Intensive care unit

*Correspondence to
Harun Düğeroğlu,
Email: Harun.dugeroglu@hotmail.com

Introduction

Uric acid is the end-product of purine metabolism in humans through the action of xanthine oxidase or xanthine dehydrogenase. Nearly 70% of the daily production of uric acid is excreted through the kidneys, while the remainder is excreted through the intestine (1). Serum uric acid concentration is affected by some factors such as excessive production, reduced glomerular filtration, renal hypoperfusion, increased tubular reabsorption, or reduced excretion. Many epidemiological studies reported the association of increases in serum uric acid levels with hypertension, dyslipidemia, liver diseases, cardiovascular diseases (CVDs), diabetes mellitus, stroke, and progression of chronic renal disease (2-6).

Acute renal injury (ARI) is a complication frequently observed in patients admitted to the hospital and is associated with high mortality and morbidity. The incidence of hospital-acquired ARI was nearly 5%-8% in epidemiological studies, increasing to 20%-35% in the intensive care unit (ICU), and 8% of these people require renal replacement therapy (7-9). Additionally, both low and high serum uric acid levels before cardiovascular surgery were shown to be risk factors for postoperative ARI (10). Hyperuricemia in patients admitted to the hospital was associated with ARI (11). The development of ARI in patients with sepsis increases patient morbidity, predicts higher mortality, and has significant effects on the function of many organs. In this study, we investigated whether increased basal uric acid levels play a significant role in predicting the development of ARI and whether it can be used as a biomarker for this.

Materials and Methods

This retrospective study included patients aged ≥ 18 years who were admitted to the ICU of Yüzüncü Yıl University Medical Faculty Hospital from September 2018 to December 2020. The inclusion criteria for the study were age ≥ 18 years and admission to the ICU due to sepsis according to the 2012 Surviving Sepsis Campaign guidelines (12). Exclusion criteria were age < 18 years, history of previous dialysis or renal transplant, kidney disease, pregnancy, and discharge from the hospital

within 10 days of admission to the ICU.

Identification of ARI was based on the presence of at least three of the following Kidney Disease: Improving Global Outcomes (KDIGO) criteria: (1) ≥ 0.3 mg/dL increase in serum creatinine level within 48 hours, (2) ≥ 1.5 times increase in serum creatinine level compared to basal values within the last 7 days, and (3) urine output < 0.5 mL/kg/h for 6 hours (13).

All data were retrospectively obtained from electronic and handwritten clinical patient records. Variables included demographic characteristics of patients (age, gender, ethnicity, and body weight), comorbidities, diabetes mellitus, hypertension, CVD, chronic obstructive pulmonary disease (COPD), medications, infection, and disease severity based on the Simplified Acute Physiologic Score II (SAPS II) (14).

SAPS II score was calculated according to the values in 12 routine physiological measurements performed within the first 24 hours of patient admission. SAPS II score was calculated from the following parameters: age, heart rate, systolic blood pressure, fever, Glasgow Coma Scale, mechanical ventilation or continuous positive airway pressure (CPAP), PaO2/FiO2, urine output, urea, sodium, potassium, bicarbonate, bilirubin, leukocyte count, chronic diseases, and type of admission. The following information was recorded on the first day of admission for every patient in the ICU: age, gender, body mass index, smoking habit, serum creatinine, urea, aspartate aminotransferase (AST), alanine aminotransferase (ALT), calcium (Ca), sodium (Na), potassium (K), albumin, uric acid, serum C-reactive protein (CRP), urine output, and duration of mechanical ventilation. The basal uric acid level was obtained from the initial data recorded when monitoring began in the ICU. The diagnosis of diabetes mellitus was made according to American Diabetes Association (ADA) criteria (15) and the diagnosis of hypertension was made according to the seventh report of the Joint National Committee (JNC) (16). CVD was accepted as the presence of cerebrovascular disease, chronic heart failure, ischemic heart disease, or history of peripheral artery diseases. COPD included emphysema and chronic bronchitis. Previous diagnosis of CVD, COPD, diabetes mellitus, and hypertension in clinical records was accepted as adequate.

Statistical Analysis

Statistical analyses were performed using IBM SPSS version 20.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to assess the normality of continuous data and variables were expressed as mean ± standard deviation (SD) or median (IQR) based on distribution. Categorical variables are reported as numbers and percentages. For the comparison of categorical variables between the groups, the chi-square test or Fisher's exact test was used. Continuous variables were compared using the Mann-Whitney U test or Student's *t* test. Spearman or Pearson correlation coefficients were used to determine the correlation between basal serum uric acid levels and clinical parameters. Multivariate logistic regression analysis was used to assess risk factors for development of septic ARI. The Hosmer-Lemeshow test was used to assess the goodness-of-fit of the model. Inequality rates and 95% confidence interval (CI) were calculated. Receiver operating characteristic (ROC) curves were used to determine the validity of basal uric acid for prediction of ARI in patients with sepsis. The cut-off value proposed for the prediction of ARI using the basal uric acid level in critical patients with sepsis was determined according to the Youden index (17). *P* value < 0.05 was accepted as statistically significant.

Results

This study included 210 patients admitted to the ICU with sepsis diagnosis from September 2018 to December 2020. All data were obtained from the database two weeks after patients were included in the study. The cohort was divided into two groups. Group 1 (n = 100) comprised sepsis patients who developed ARI. Group 2 (n = 110) comprised patients who did not develop sepsis. The demographic and clinical features of the population according to ARI development are defined in Table 1. Patients developing ARI were staged according to KDIGO. Accordingly, 46% (n = 46) had developed stage 1, 34% (n = 34) developed stage 2, and 20% (n = 20) developed stage 3 ARI.

No significant differences were observed between the two groups in terms of gender, body mass index, ALT, AST, Na, K, and CRP. The SAPS II values in patients admitted to the ICU with sepsis diagnosis developing ARI during follow-up were higher than the SAPS II values in patients who did not develop ARI and this difference was statistically significant (38.13 ± 14.52 and 28.22 ± 8.98; *P* < 0.001). Basal serum uric acid level was significantly higher in patients with ARI compared to patients without ARI (7.82 ± 1.93 mg/dL and 5.43 ± 1.16 mg/dL; *P* = 0.001). Additionally, the serum albumin values in patients with ARI were lower compared to patients without ARI (3.31 ± 0.53 g/dL and 3.44 ± 0.41 g/dL; *P* = 0.042) (Table 1).

Logistic regression analysis found that SAPS II, albumin, and basal serum uric acid values were independently associated with the development of ARI in patients with sepsis (Table 2).

Basal serum uric acid values were positively correlated with SAPS II score (Pearson r = 0.707, *P* < 0.0001). No correlation was identified between basal uric acid level and creatinine or estimated glomerular filtration rate (eGFR). There was no correlation between basal serum uric acid and clinical parameters.

ROC curve analysis found that the cut-off value of 6.95 mg/dL for basal serum uric acid had 82% sensitivity and

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Table 1. Comparison of Demographic and Clinical Features of Patients with Sepsis in the Intensive Care Unit between the Study Groups

	Group 1 (With ARI, n=100)	Group 2 (Without ARI, n=110)	P Value
Age (year)	67.4±16.5	65.7±14.8	0.743
Gender (male/female), n (%)	44/56 (44/56)	48/62 (43.6/56.4)	0.834
Body mass index, kg/m²	27.62±2.51	28.73±3.82	0.648
Smoking history, n (%)	26 (26)	28 (25.45)	0.236
Hypertension, n (%)	56 (56)	62 (56.36)	0.674
Diabetes mellitus, n (%)	22 (22)	24 (21.81)	0.576
Heart failure, n (%)	8 (8)	10 (9.09)	0.381
COPD, n (%)	18 (18)	20 (18.18)	0.452
ACEI/ARB, n (%)	48 (48)	44 (40)	0.192
Source of infection			
Lung, n (%)	34 (34)	38 (34.54)	0.722
Urinary tract, n (%)	26 (26)	28 (25.45)	0.615
Intra-abdominal, n (%)	20 (20)	22 (20)	1.000
Others, n (%)	20 (20)	22 (20)	1.000
Basal SAPS II	38.14±14.52	28.22±8.98	<0.001*
Basal invasive mechanical ventilation status, n (%)	24 (24)	32 (29.09)	0.093
Duration of invasive mechanical ventilation, hour	118±97	122±86	0.213
Laboratory values at the time of admission			
Creatinine, mg/dL	0.84±0.26	0.81±0.22	0.584
International normalized ratio	1.08±0.61	1.09±0.73	0.625
aPTT (s)	46±37	44±38	0.467
ALT, U/L	58±34	60±42	0.293
AST, U/L	60±33	59±38	0.621
Total bilirubin, mg/dL	1.72±1.23	1.64±1.13	0.633
Ca, mg/dL	8.91±0.82	9.13±0.91	0.709
Na, mEq/L	141±5.42	140±5.83	0.366
Potassium (K), mEq/L	4.48±0.73	4.36±0.81	0.746
Albumin, g/dL	3.31±0.53	3.44±0.41	0.042*
Basal uric acid, mg/dL	7.82±1.93	5.43±1.14	0.001*
CRP, mg/L	244±118	246±122	0.436

ARI: acute renal injury, COPD: chronic obstructive pulmonary disease, SAPS II: simplified acute physiologic score II, ACEI: angiotensin converting enzyme inhibitors, ARB: angiotensin receptor blocking agents, aPTT: activated partial thromboplastin time, ALT: alanine aminotransferase, AST: aspartate aminotransferase, CRP: C-reactive protein, Ca: calcium, Na: Sodium; K: Potassium.
* $P<0.005$.

Table 2. Identification of Independent Risk Factors for Predicting Acute Renal Injury in Patients With Sepsis Using Multivariate Logistic Regression Analysis

	Univariate (OR, 95% CI)	P Value	Multivariate (OR, 95% CI)	P Value
SAPS II	3.78 (2.25-5.18)	<0.001	2.98 (1.99-6.14)	0.02
Albumin	0.88 (0.62-0.94)	<0.001	0.99 (0.82-1.43)	0.07
Basal uric acid	5.32 (2.85-8.59)	<0.001	5.06 (1.82-14.21)	<0.001

SAPS II: Simplified Acute Physiologic Score II.

88.5% specificity for prediction of ARI (AUC=0.847, 95% CI: 0.770–0.924) (Figure 1).

Discussion

This retrospective study identified that increases in serum uric acid levels in patients admitted to the ICU with sepsis diagnosis were associated with the development of ARI. The etiology of ARI has a broad spectrum and many mechanisms including ischemic/hypoxic, nephrotoxic, and inflammatory processes contribute to the development of ARI. ARI develops in nearly 30% of septic patients and the incidence of ARI in the ICU reaches 50% (18). Additionally, in-hospital mortality associated with severe ARI is significantly higher in
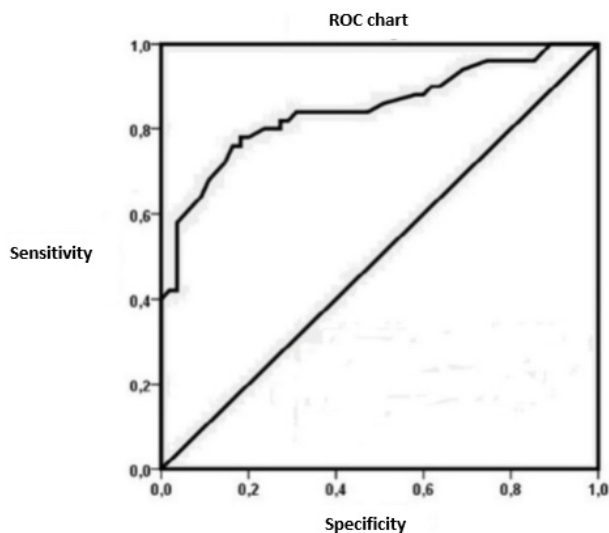
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Figure 1. ROC Analysis Curve for the Cut-off Value, Sensitivity, and Specificity of Basal Serum Uric Acid in Predicting ARI

septic patients compared to patients who are not septic (70.2% and 51.8%, respectively) (9,18). The mechanism for the increase in uric acid in sepsis is still not fully known. It may be related to increased uric acid production or reduced excretion. Ischemia or hypoxia may trigger severe sepsis and septic shock; this may further increase the conversion of xanthine/hypoxanthine to uric acid mediated by xanthine oxidase activation in microvascular endothelium (19,20). Therefore, an increase in uric acid production occurs. Hyperuricemia may reduce nitric oxide production by reducing endothelial nitric oxide synthase and increasing levels of inflammatory cytokines (IL-6, TNF-α), intercellular adhesion molecule 1, and vascular cell adhesion molecule 1, known as adhesion molecules (21,22). In this situation, the vascular tone of the endothelial system cannot be regulated. These events cause a wide range of pathophysiological processes and dysfunctions in internal organs including the kidneys (23).

The increased uric acid level may cause ARI through several mechanisms. These mechanisms range from direct tubular toxicity due to injury induced by uric acid crystals to secondary injury linked to vasoactive mediator release and oxidative stress (23,24). Increased serum uric acid level may cause ARI due to renal vasoconstriction in response to activation of the renin-angiotensin system, catecholamine release, oxidative stress, proinflammatory marker release, and reduced nitric oxide levels (25). In experimental models of ARI, increased serum uric acid further increased renal injury through proinflammatory pathways involving chemokine expression with leukocyte infiltration (26,27). As a result, we researched the potential effect of basal uric acid level for prediction of the development of ARI among patients admitted to the ICU with sepsis diagnosis.

Uric acid may cause kidney injury due to endothelial dysfunction, vasoconstriction, oxidative stress, and intra-tubular obstruction. As a result, uric acid may predict the risk of ARI in septic patients. In patients with sepsis, development of ARI causes an independent and significant increase in the risk of in-hospital mortality and is associated with lengthened ICU and hospital stays (27).

No correlation was found between increased serum uric acid and sepsis prognosis. However, hyperuricemia was correlated with SAPS II, which is used to rate the severity of sepsis in ICU patients. Similarly, several studies reported that serum uric acid levels may reflect the severity and prognosis of sepsis (28-30).

High preoperative serum uric acid levels before cardiovascular surgery and cardiac catheterization were reported to be associated with postoperative ARI (10, 31,32). Additionally, increased serum uric acid levels increase the risk of ARI caused by contrast agents (33,34). These studies showed that an increased serum uric acid level may predict ARI in patients with sepsis, which is consistent with our study.

Study Limitations
There are some limitations to this study. The first one is related to the results based on the retrospective and single-center nature of the study. Second, the sample size in our study is relatively small. The inclusion of more subjects in the study can increase the generalizability and accuracy of the results. Third, it was not possible to define the cause-and-effect relationship between hyperuricemia and ARI in patients with sepsis. Other possible limitations are that patients were only monitored for 10 days and that uric acid values were not followed to show whether there were potential changes that may reflect the patient's status. The Acute Physiology and Chronic Health Evaluation II (APACHE II) is the most frequently used system to assess disease severity in the ICU; however, we used the SAPS II described in 1984 instead of the APACHE II system.

Conclusion
It can be concluded that an increased basal serum uric acid level observed in patients admitted to the ICU with sepsis may be an important biomarker for predicting the development of ARI.

Informed Consent

An informed consent was obtained from all participants.

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