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The predictive value of serum uric acid in development of acute kidney injury and mortality in patients with sepsis

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ABSTRACT

Introduction: Acute kidney injury (AKI) and sepsis are significant causes of morbidity and mortality in intensive care units. Therefore, early screening of high-risk individuals is critical for preventing AKI and improving outcomes.
Objectives: To examine the possible involvement of uric acid in predicting AKI and mortality in septic patients.
Patients and Methods: A prospective study recruited 400 patients with sepsis based on the quick Sequential Organ Failure Assessment (qSOFA) criteria who were hospitalized in the intensive care unit (ICU). Patients were categorized into two groups depending on their uric acid levels; those with a serum uric acid ≥7 mg/dL and those with a serum uric acid <7 mg/dL.
Results: A total of 400 septic patients were included in this study. Among them, 52.5% (210/400) patients had hyperuricemia during admission to the ICU. A total of 177/400 (44.2%) patients developed AKI. The likelihood of having hyperuricemia in association with AKI was 65.6%. Meanwhile, the likelihood of having a uric acid level of less than 7 mg/dL in association with AKI was 23.9% ($P<0.001$). The mortality rate in the hyperuricemia group was substantially greater than in the normal uric acid level group ($P<0.001$). Uric acid levels higher than 7 mg/dL were significantly associated with AKI by multivariate logistic regression ($P=0.002$). Receiver operating characteristic (ROC) curves revealed that uric acid has a high predictive value for AKI and ICU mortality in patients with sepsis.
Conclusion: Serum uric acid could be a marker to predict AKI and mortality in patients with sepsis.

Implication for health policy/practice/research/medical education:
Serum uric acid can be utilized as an oxidative stress marker since it acutely stimulates many transcription factors. The study was conducted on 400 septic patients admitted to intensive care unit (ICU). The results suggested that uric acid levels during ICU admission are related to an elevated risk of early death, and acute kidney injury in patients with sepsis. This low-cost biomarker could aid in the prediction of disease severity.

Introduction

Acute kidney injury (AKI) is prevalent in critically ill patients, especially in the presence of sepsis and after the administration of several nephrotoxins, including contrast agents. The incidence rate and severity of AKI are related to the severity of the underlying sepsis. Both AKI and sepsis are significant causes of morbidity and mortality in intensive care units (ICUs). Therefore, early screening of high-risk individuals is critical to preventing AKI and improving outcomes (1–3).

Biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) (4) and cell cycle arrest indicators tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP-7) (5) have been investigated for the early diagnosis of kidney dysfunction. However, all of these indicators are costly, and their clinical use appears to be limited.

Uric acid is a byproduct of purine degradation, and the majority of it is eliminated in urine. In sepsis, hyperuricemia develops as a result of both increased production and reduced excretion. The method by which uric acid induces AKI may be attributed to the activation

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of pro-inflammatory systemic cytokines, such as tumor necrosis factor, as well as oxidative stress (6). Additionally, uric acid crystal formation obstructs renal tubules, producing direct tubular damage (7).

Objectives

Numerous studies have found a correlation between hyperuricemia and chronic systemic diseases such as chronic kidney diseases (CKD), hypertension, diabetes, and cardiovascular diseases (8–10). In addition, the uric acid level has been demonstrated to be an independent predictor of AKI in hospitalized patients (11), as well as a predictor of mortality in critically ill septic patients (12). The current study was conducted to examine the possible involvement of uric acid in predicting AKI and death in patients with sepsis.

Patients and Methods

Study design

This was a prospective study conducted in the Critical Care Unit of Kasr Al-Ainy hospital, Cairo University from July 2019 to May 2021. The study recruited 400 patients over the age of 18 who were admitted to a medical or surgical ICU with a clinical diagnosis of sepsis based on the quick Sequential Organ Failure Assessment (qSOFA) criteria. Patients were excluded from the study if they had an anticipated ICU stay shorter than 24 hours, end-stage renal failure, gout, or hyperuricemia-causing medications. Additionally, pregnant women were excluded from participation.

Once the patient satisfied the inclusion criteria, consent was received from the study participants. At the time of presentation to the ICU, patients' characteristics such as age, gender, primary diagnosis of hospital admission, and comorbidities were gathered. Vital signs at admission (pulse rate, breathing rate, blood pressure, and oxygen saturation) were recorded.

The qSOFA score and Acute Physiology Health Disease Classification System II (APACHE II) were calculated. The qSOFA score is composed of three criteria (systolic blood pressure ≤100 mm Hg, respiratory rate ≥22 breaths per min, and Glasgow Coma Scale <15). A score of 2 or 3 points indicates a significant likelihood of a bad prognosis in individuals with sepsis. Within 48 hours after admission to the ICU, blood samples were taken for serum uric acid, electrolytes, albumin, complete blood count, renal function tests, and arterial blood gases. A chest X-ray was performed.

Patients were divided into two groups depending on their uric acid levels: those with a serum uric acid level ≥ 7 mg/dL and those with a serum uric acid level <7 mg/dL. Uric acid was used to predict AKI and mortality. AKI was defined as an increase in serum creatinine (sCr) of 0.3

mg/dL (26.5 mol/L) within 48 hours, or a rise in sCr to 1.5 times the baseline that occurred within the preceding seven days, using Kidney Disease Improving Global Outcomes guidelines (13).

All patients were followed up on until they were discharged from the hospital or died for the development of AKI (primary outcome). The prevalence of acute respiratory distress syndrome (ARDS), need for renal replacement therapy, duration of mechanical ventilation, length of ICU stay, and usage of inotropes were documented as secondary outcomes.

Statistical analysis

The mean and standard deviation were used to describe the quantitative data, while in categorical data; the frequency (count) and relative frequency (%) were used. The non-parametric Mann-Whitney U test was applied to compare quantitative variables. The chi-square (2) test was used to compare categorical data. When the predicted frequency is less than 5, the exact test was applied instead. The Spearman's correlation coefficient was used to calculate correlations between quantitative variables. To identify independent predictors of AKI, logistic regression was used. The area under the curve (ROC; receiver operating characteristic) was used to identify the appropriate cut-off value for uric acid levels for prediction of AKI, ARDS, and mortality. Statistical significance was defined as P values less than 0.05.

Results

All patients in this study were above 18 years of age. Among the 400 patients, 207 were males and 193 were females, with a mean age of 61.96 ± 16.74 (Table 1). They were divided into two groups depending on their uric acid levels: those with a serum uric acid level ≥7 mg/dL (including 210 patients) and those with a serum uric acid level <7 mg/dL (including 190 patients).

Between the two groups, the congestive heart failure, CKD, and malignancy frequencies were higher in the hyperuricemia group (25 (11.9%) versus 14 (7.4%), 30 (14.3%) versus 6 (3.2%), and 34 (16.2%) versus 16 (8.4%), $P<0.001$ for all). While the frequency of surgery was lower in the hyperuricemia group than those with normal uric acid levels, 5 (2.4%) versus 7 (3.7%), $P<0.001$. There was no statistically significant difference in gender distribution, diabetes, or hypertension ($P=0.791$ and $P=0.068$, respectively; Table 2).

The mean age, APACHE and qSOFA scores were greater in the hyperuricemia group than those with normal uric acid levels. The difference between the two groups was extremely significant ($P<0.001$). The current study found higher blood urea nitrogen (BUN) levels (67.11 ± 36.93 mg/dL versus 16.64 ± 8.38 mg/dL, $P<0.001$) and lower

Table 1. Demographic and baseline characteristics of all patients

	No.	%
Female	193	48.3%
Male	207	51.7%
CKD	36	9.0%
Hypertensive	88	22%
Diabetic	37	9.3
Malignancy	50	12.5%
Surgery	12	3.0%
Congestive heart failure	39	9.8%
Need for vasopressors	189	47.3%
Need for mechanical ventilation	213	53.2. %
RRT	76	19.0%
ARDS	88	22.0%
AKI	177	44.2 %
	Mean	**Standard deviation**
Age (y)	61.96	16.74
APACHE	19.96	10.57
qSOFA	1.78	0.85
Albumin (g/dL)	3.21	0.88
BUN (mg/dL)	43.14	37.21
Uric acid (mg/dL)	7.47	3.47
PO4 (mg/dL)	3.52	2.08
Duration of mechanical ventilation	5.42	7.13
ICU stay	8.77	8.23

CKD: Chronic kidney diseases, RRT: Renal replacement therapy, ARDS: Acute respiratory distress syndrome, AKI: Acute kidney injury, APACHE: Acute Physiology Health Disease Classification System II, qSOFA: Quick Sequential Organ Failure Assessment, BUN: Blood urea nitrogen.

albumin levels (2.64 ± 0.60 g/dL versus 3.84 ± 0.69 g/dL, $P<0.001$) among the hyperuricemia group when compared to patients with normal uric acid levels. There

was no considerable variation in mean phosphorus levels between both groups ($P=0.060$; Table 3).

A total of 177 (44.2%) of 400 patients developed AKI. Nineteen percent of all patients needed renal replacement treatment (RRT). The likelihood of having hyperuricemia in association with AKI was 65.6 percent. Meanwhile, the likelihood of having a uric acid level of less than 7 mg/dL in association with AKI was 23.9 percent (P value <0.0001). Additionally, the requirement for vasopressors was considerably greater in the hyperuricemia group than in those with normal uric acid levels: 161 (76.7%) versus 28 (14.7%; $P<0.001$). The incidence of ARDS was substantially different between the two groups (hyperuricemia group: 35.2%, normal uric acid group: 7.4%, $P<0.001$; Table 4). Moreover, the mean duration of mechanical ventilation (MV) and ICU stay was substantially longer in the hyperuricemia group than in the normal uric acid group ($P<0.001$; Table 5).

A total of 188 of 400 patients died. Out of non-survivors, 162 (77.1%) patients had hyperuricemia, whereas 26 (13.7%) had normal uric acid levels with a highly statistically significant difference ($P<0.001$; Table 6).

There were significant positive correlations between serum uric acid, BUN, creatinine, APACHE, qSOFA scores, duration of MV, and ICU stay. While uric acid and albumin levels were shown to have a negative correlation ($P<0.001$ for all; Table 7).

Univariate and multivariate logistic regression were used

Table 2. Gender and co morbidities of both groups

		Uric acid				P value
		<7 g/dL		≥7 g/dL		
		No.	%	No.	%	
Gender	Female	93	48.9%	100	47.6%	0.791
	Male	97	51.1%	110	52.4%	
Comorbid disease	CKD	6	3.2%	30	14.3%	<0.001
	Malignancy	16	8.4%	34	16.2%	
	Surgery	7	3.7%	5	2.4%	
	Congestive heart failure	14	7.4%	25	11.9%	
	Hypertensive	44	23.2%	44	21.0%	0.791
	Diabetic	16	8.4%	21	10.0%	0.068

Table 3. Age, scoring system and basic laboratory investigations of both groups

	Uric acid				P value
	<7 g/dL		≥7 g/dL		
	Mean	SD	Mean	SD	
Age (y)	55.74	17.96	67.59	13.28	<0.001
APACHE	12.81	6.85	26.42	9.08	<0.001
qSOFA	1.26	0.55	2.25	0.81	<0.001
BUN (mg/dL)	16.64	8.38	67.11	36.93	<0.001
Albumin (g/dL)	3.84	0.69	2.64	0.60	<0.001
PO4 (mg/dL)	3.47	0.99	3.57	2.71	0.060

QSOFA: Quick Sequential Organ Failure Assessment, BUN: Blood urea nitrogen.

Table 4. Distribution of AKI, ARDS and need for vasopressors among both groups

		Uric acid				*P* value
		<7 g/dL		≥7 g/dL		
		No.	%	No.	%	
AKI	Yes	49	23.9%	128	65.6%	<0.001
	No	156	76.1%	67	34.4%	
ARDS	Yes	14	7.4%	74	35.2%	<0.001
	No	176	92.6%	136	64.8%	
Need for vasopressors	Yes	28	14.7%	161	76.7%	<0.001
	No	162	85.3%	49	23.3%	

ARDS: Acute respiratory distress syndrome, AKI: Acute kidney injury.

Table 5. Duration of mechanical ventilation (MV) and ICU stay of both groups

	Uric acid				*P* value
	<7 g/dL		≥ 7 g/dL		
	Mean	SD	Mean	SD	
Duration of MV	1.79	4.50	8.70	7.48	<0.001
ICU stay	5.04	4.38	12.15	9.38	<0.001

Table 6. Mortality rate of both groups

		Uric acid				*P* value
		<7 g/dL		≥7 g/dL		
		No.	%	No.	%	
Outcome	Died	26	13.7%	162	77.1%	<0.001
	Survivor	164	86.3%	48	22.9%	

to investigate independent risk variables for AKI (Table 8). Contrast agent [odds ratio (OR) 12.714, 95% confidence interval (CI) 6.476-24.959], nephrotoxic medication (OR: 12.410, 95% CI 6.466-23.817), CKD (OR: 4.2, 95% CI 1.8 -9.6), and uric acid level higher than 7 mg/dL (OR: 6.08, 95% CI 3.9-9.4) were significantly associated with AKI. On other hand, male gender, diabetes mellitus, hypertension, surgery, congestive heart failure, and malignancy were not significantly associated with AKI. Contrast agent, nephrotoxic medication, CKD and uric acid levels higher than 7 mg/dL, maintained statistical significance in multivariate logistic regression analysis [27.575 (8.551-88.925), *P*<0.001, 21.147 (7.029-63.621), *P*<0.001, 4.5 (1.5-13.5), *P*=0.007, 3.2 (1.5-6.9), *P*=0.002, respectively].

Table 7. Correlation between uric acid and other parameters

	Uric acid	
	Correlation Coefficient	*P* value
Albumin	-0.722	<0.001
BUN	0.800	<0.001
Creatinine	0.776	<0.001
APACHE	0.706	<0.001
qSOFA	0.690	<0.001
Duration of MV	0.646	<0.001
ICU stay	0.594	<0.001

APACHE: Acute Physiology Health Disease Classification System II, qSOFA: Quick Sequential Organ Failure Assessment, BUN: blood urea nitrogen, MV: mechanical ventilation.

ROC was constructed to determine the best uric acid cutoff value associated with AKI, ARDS, and mortality (Figure 1A-C). The value of 7.25 mg/dL was the best uric acid value associated with AKI (91.3% sensitivity and 89.4% specificity; *P*<0.001). In addition, the best uric acid cutoff value associated with ARDS was 8.7 mg/dL (77.3% sensitivity and 75.3% specificity; *P*<0.001). Finally, the best uric acid cutoff value associated with ICU mortality was 6.75 mg/dL (sensitivity = 91%, specificity = 76.9%, UAC = 0.916).

Discussion

The current study found that 52.5% of patients had high uric acid levels at the time of ICU admission. Furthermore, hyperuricemia was linked to a higher risk of death, AKI, and ARDS when contrasted to normal uric acid levels. The mechanisms that cause elevated uric acid levels in sepsis are unclear, but they might be related to enhanced synthesis and reduced excretion. When oxidant levels surpass antioxidant levels, oxidative stress ensues, which can lead to organ damage and enhance the conversion of xanthine/hypoxanthine to uric acid by activating xanthine oxidase in the microvascular endothelium. Whatever the mechanism, hyperuricemia is significantly linked with higher mortality and poor clinical outcome in septic patients.

In this prospective study, multivariate logistic regression

Table 8. Univariate and multivariate logistic regression analysis for risk factors for AKI development
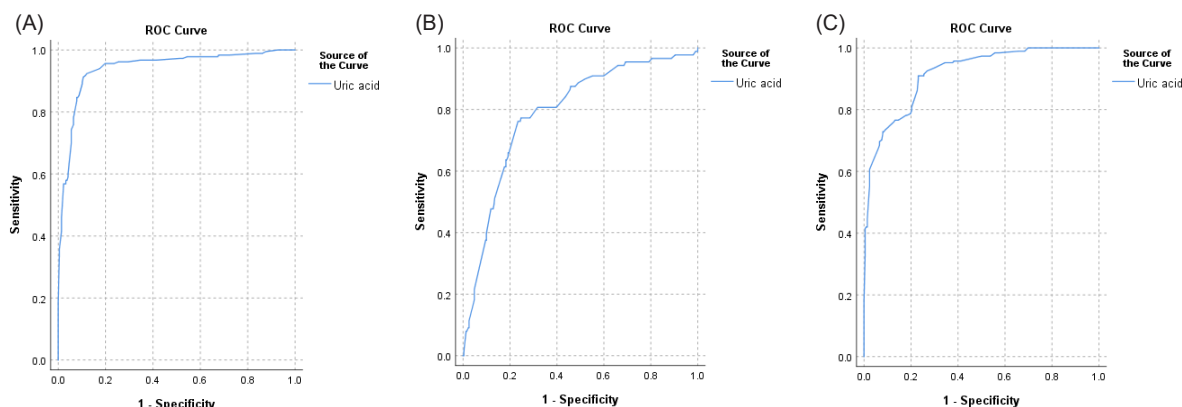
		Univariate analysis				Multivariate analysis			
		P value	OR	95% CI		*P* value	OR	95% CI	
				Lower	Upper			Lower	Upper
AKI	Male Sex	0.794	1.054	0.711	1.562				
	DM	0.056	1.479	0.990	2.211				
	HTN	0.314	1.225	0.825	1.818				
	Contrast agents	**<0.001**	12.714	6.476	24.959	**<0.001**	27.575	8.551	88.925
	Nephrotoxic drugs	**<0.001**	12.410	6.466	23.817	**<0.001**	21.147	7.029	63.621
	CKD	**<0.001**	4.2	1.8	9.6	**0.007**	4.5	1.5	13.5
	Surgery	0.059	0.229	0.049	1.058				
	Malignancy	0.065	1.758	0.965	3.202				
	Uric acid ≥ 7 g/dL	**<0.001**	6.08	3.9	9.4	0.002	3.2	1.5	6.9

analysis was applied to examine independent risk variables for AKI, excluding hypertension, congestive heart failure, and malignancy, all of which can cause hyperuricemia. Uric acid levels greater than 7 mg/dL were significantly associated with AKI (OR: 3.2, 95% CI: 1.5-6.9). Moreover, the value of 7.25 mg/dL was the best uric acid value associated with AKI (91.3% sensitivity and 89.4% specificity, $P < 0.001$), suggesting that uric acid levels in sepsis patients can be employed to predict AKI.

This finding is supported by the research of Akbar et al (12). They conducted a prospective study on 144 patients with sepsis and found that uric acid levels ≥ 7 mg/dL were independent risk variables for AKI as well as AKI-associated death on ICU admission. The likelihood of having hyperuricemia with AKI is around 68.5%, while the likelihood of having hyperuricemia without AKI is roughly 31.5 percent. These probabilities are statistically significant with a *P* value of <0.001. Moreover, in 2017, Xu et al published a meta-analysis of 18 cohort studies involving 75 200 participants. They discovered that hyperuricemia is a distinct predictor of AKI (14). Similarly, Yeter et al (15) found that uric acid levels of more than 7 mg/dL were linked with AKI in critically ill individuals,   *P*<0.001).

Patients with sepsis are at risk of developing AKI because systemic hypotension reduces blood flow to the kidney, which may be a primary reason for kidney dysfunction (16). Moreover, AKI can be induced by hyperuricemia by several pathways, ranging from direct tubular toxicity caused by crystal-induced damage (7) to indirect injury caused by the production of vasoactive mediators, pro-inflammatory markers, and oxidative stress (6). Uric acid can potentially induce AKI due to renal vasoconstriction caused by renin-angiotensin system activation, catecholamine release, and decreased nitric oxide levels (17).

According to the findings of this study, nephrotoxic medications, contrast agents, and CKD are all independent risk factors for AKI. These results are in agreement with previous studies (18,19). To avoid AKI, more careful methods for kidney preservation (such as hydration or N-acetylcysteine administration) are necessary for the treatment of septic patients before contrast agent exposure. Conversely, Yeter et al (15) found that the contrast agent was not a statistically significant risk factor for AKI incidence. The discrepancy might be attributed to the low number of individuals who used a contrast agent in the other trial.

Figure 1. ROC curve for best cutoff value of uric acid levels associated with (A) AKI, (B) ARDS, and (C) mortality.

Additionally in the current study, age and gender distribution were not predictors of AKI in septic patients. A study by Suh et al (20), found no significant variations in the number of male patients with AKI rather than those without. While they observed that older age in patients with septic shock was a risk factor for the incidence of kidney dysfunction.

It is worth noting that the best serum uric acid value related to mortality in the current study was 6.75 mg/dL (sensitivity=91% and specificity=76.9%, UAC=0.916). This suggests that uric acid levels in septic patients may be an early prognostic marker. Similar to the literature, others show that hyperuricemia is linked to a higher risk of death (12,21). Furthermore, in a study of 1,140 consecutive patients having coronary artery bypass grafting, Hillis et al (22) found a 1.5-fold rise in the risk of all-cause mortality for every 1.68-mg/dL rise in uric acid level over a 4.5-year median follow-up.

On the contrary, in a retrospective cohort analysis of 2,123 critically ill patients, Chen et al (23) found no relation between uric acid and 90-day mortality (Hazard ratio 1.00, 95% CI 0.98–1.03, P=0.6835), indicating that uric acid showed weak discriminative abilities for predicting 90-day mortality.

In the present study, a substantial variation in the development of ARDS was observed between the two groups. In addition, the best uric acid cutoff value for ARDS was 8.7 mg/dL (77.3% sensitivity and 75.3% specificity; P<0.001). These findings are consistent with those reported by Bhandary et al (21). They demonstrated that 87.5% of the septic patients (based on qSOFA criteria) with hyperuricemia had ARDS. The possible explanation for the link between hyperuricemia and ARDS is a rise in serum uric acid levels, particularly in the context of hypoxia and systemic inflammation. In contrast, the study by Akbar et al (12) found no association between increased uric acid levels at presentation and ARDS in sepsis.

One of the most significant findings in this investigation was the positive relationship between hyperuricemia and APACHEII score. Similarly, Chuang et al (24) suggested that serum uric acid levels are associated substantially with serum total antioxidant capacity and APACHEII scores in septic patients. In addition, the present study demonstrated that the duration of MV and ICU stay were both strongly associated with hyperuricemia. These findings were supported by previous research, which found that a serum uric acid level of 6.9 mg/dL is related to prolonged duration of MV and ICU hospitalization in individuals with respiratory diseases (25).

Conclusion
This study found that uric acid levels during ICU admission are related to an elevated risk of early death, ARDS, and AKI in patients with sepsis. This low-cost biomarker could aid in the prediction of disease severity as evaluated by the APACHEII, QSOFA scores, prolonged duration of mechanical ventilation, and ICU hospitalization that could benefit from intensive management.

Limitations of the study
This study had some limitations. Firstly, uric acid levels were obtained within 48 hours of admission; follow up of uric acid during the ICU stay may have improved the validity of the results. Secondly, this study evaluated the prognostic role of serum uric acid for only short-term outcomes.

Author's contribution
DAM is the single author of the paper.

Conflicts of interest
None.

Ethical issues
The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Faculty of Medicine, Cairo University approved this study. Accordingly, written informed was consent taken from all participants before any intervention. Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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