



Association between Serum Uric Acid and Mortality Rate among Admitted Patients in Intensive Care Unit

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Abstract

Background: Patients admitted to the Intensive Care Unit (ICU) generally exhibit high mortality rates, of which identifying associated factors can lead to better clinical management. The current study investigated the association between serum uric acid levels and mortality rates in patients admitted to ICU.

Methods: In this cross-sectional study, demographical, clinical, and laboratory data of 126 patients admitted into the ICU of Razi Hospital, Rasht, Iran, were recorded. Also, the serum levels of creatinine and uric acid were evaluated. The severity score and mortality estimation was assessed using the Acute-Physiology-and-Chronic-Health-Evaluation-II (APACHE II) score. Data was analyzed using SPSS software, version 21, and the significant level was set at 0.05.

Results: About 57.9% of the patients were male and 42.1% were female. The mean age of the patients was 56.46 ± 17.02 years. The mean level of uric acid was 4.13 ± 1.94 mg/d. Among different cause of ICU admission, surgery was the leading cause (38.89%), of which 69.05% were discharged, and the average ICU stay was 10.87 ± 8.75 days. Patients requiring ventilators or vasopressors had significantly higher mortality rates ($p < 0.001$). Higher APACHE II scores, longer ICU stays, and elevated uric acid levels were strongly associated with increased prevalence of mortality ($p < 0.05$). Logistic regression analysis confirmed that the need for ventilators, vasopressors, and elevated uric acid levels significantly raised the death outcome among ICU patients with hyperuricemia ($p < 0.05$).

Conclusion: The findings demonstrated that elevated serum uric acid levels are significantly associated with increased mortality rates among patients admitted to the ICU, which suggests that monitoring and managing hyperuricemia may help improve patient outcomes in critical care settings.

Keywords: Acute physiology and chronic health evaluation, Intensive care unit, Mortality, Serum uric acid

Introduction

Uric acid, a product of purine metabolism, has been recognized as both an antioxidant and a pro-oxidant, depending on its concentration and the cellular environment (1,2). Studies have revealed a notable prevalence of hyperuricemia among critically ill patients, with estimates ranging from 20 to 40%, depending on the population studied and the defined threshold for elevated uric acid levels (3,4). The etiology of hyperuricemia in critically ill patients is multifactorial, encompassing increased production and decreased excretion of uric acid (5). Factors contributing to elevated uric acid levels include tissue hypoxia, increased cell turnover, renal dysfunction, and medications that interfere with uric acid metabolism or excretion (6).

Uric acid may serve as a marker of oxidative stress, which is known to play a crucial role in the development and progression of multiple organ dysfunction syndrome, a leading cause of death, especially among vulnerable patients such as those admitted in the Intensive Care Unit (ICU) (7,8). Patients with severe conditions, such as respiratory dysfunction, cardiovascular disease, septicemia, major hemorrhages, diabetic ketoacidosis, kidney failure, *etc.*, typically require intensive care and monitoring (9-13). Elevated uric acid levels have been associated with longer ICU stays, increased mechanical ventilation duration, and a higher incidence of acute kidney injury and multiple organ failure in vulnerable patients (3,14).

Additionally, hyperuricemia has been linked to endothelial dysfunction, inflammation, and activation of the renin-angiotensin-aldosterone system, all of which can contribute to adverse outcomes in critical illness (15). Studies have demonstrated a positive correlation between elevated uric acid levels and increased short-term and long-term mortality rates (16,17). To quantify the severity of illness and predict patient outcomes based on various physiological and clinical parameters, the Acute Physiology and Chronic Health Evaluation II (APACHE II) is a widely used severity-of-disease classification system in ICU worldwide (18). The APACHE II score has demonstrated good discriminative ability in predicting hospital mortality across various patient populations and critical care settings.

Despite developing newer scoring systems, APACHE II remains a cornerstone in critical care assessment due to its simplicity, widespread familiarity, and robust validation across diverse patient populations (19,20). Regardless of the growing body of evidence supporting the association between hyperuricemia and adverse outcomes in ICU patients, it remains unclear whether elevated uric acid levels are simply a marker of disease severity or play a causal role in the pathogenesis of critical illness complications. Therefore, the current study investigated the association between serum uric acid levels and mortality rate in ICU patients by considering related risk factors.

Materials and Methods

Study design and sample size

In this cross-sectional study, 126 patients who were admitted at the ICU of Razi Hospital, Rasht, Iran, were enrolled. Patients were selected using a convincing sampling method, and the sample size was calculated following the Pehlivanlar-Kucuk *et al's* study (21) by considering a 95% Confidence Interval (CI) with a power of study of 90%. The study was confirmed by the ethical committee of the Guilan University of Medical Sciences, Rasht, Iran [IR.GUMS.REC.1399.591]. Dialysis patients, patients with acute renal failure, patients with chronic renal failure (glomerular filtration rate less than 60%), pregnant women, those with kidney trauma, and patients who received nephrotoxic drugs were excluded from the study.

Data collection

Data of age, gender, number of days in ICU, underlying disease, use of a ventilator, need for vasopressor, and patient outcome (discharged or death) were recorded. The serum level of creatinine (0.7–1.3 mg/dL for men and 0.5–1.1 mg/dL for women) and uric acid (3.5–7.2 mg/dL for men and 2.6–6.0 mg/dL for women) within the first 24 hr of ICU admission were evaluated via BT3500 auto analyzer (Biotechnica, Italy) using Pishtaz Teb kit (Pishtaz Teb, Iran) at the central laboratory of the Razi Hospital.

The APACHE II score was calculated using 12 routine physiological measurements, including vital signs [temperature, mean arterial pressure, heart rate,

respiratory rate, oxygenation, and Glasgow Coma Scale (GCS)] and laboratory findings [arterial pH, serum sodium, serum potassium, serum creatinine, hematocrit, and white blood cell count]. The higher score indicated a more severe condition and a higher risk of mortality (scoring from zero to 71) (22).

Statistical analysis

Statistical results were reported by number, percentages, mean $\pm$ standard deviation (SD), median, and Interquartile Range (IQR). Chi-square, Mann-Whitney U, and Fisher's exact tests were employed to compare the variables. To evaluate the association between serum uric acid levels and mortality rate, multivariate logistic regression was performed by 95%CI and reported as Odds Ratio (OR). Data was analyzed using SPSS version 21 (IBM Corp., Armonk, NY, USA) with a significant level <0.05 .

Results

The mean age of the patients was 56.46 ± 17.02 years (18-85 years), and 57.94% were male ($n=73$). The mean duration of ICU stay was 10.87 ± 8.75 days (2-45 days). Most patients were admitted to the ICU for non-surgical causes (61.11%), and 49 patients (38.89%) were admitted to the ICU after surgery. Out of the total participants, 43.65% stayed in the ICU for one week. About 62.70% required ventilator, and 23.02% needed vasopressor. Among the ICU patients, 60.32% had APACHE II scores above 20, and 69.05% were discharged from the ICU (Table 1). The mean serum levels of creatinine and uric acid were 0.97 ± 0.19 mg/dL (0.57-1.40 mg/dL) and 4.13 ± 1.94 mg/dL (5.20-1.10 mg/dL), respectively.

The prevalence of diabetes and gastrointestinal diseases was higher in patients with death outcomes, while those admitted in the ICU for post-surgery complications, had the highest discharge rate (85.71%) ($p=0.028$). The need for ventilators and vasopressors significantly increased mortality risks ($p<0.001$). APACHE II scores were strongly correlated with mortality rate among the ICU patients ($p<0.001$), of whom all patients with APACHE II score <20 were discharged, while all those with score >29 terminated in death. The prevalence of death outcome was significantly higher among patients with APACHE II score between 25 to 29 ($p<0.001$) (Table 2).

Table 1. The frequency of clinical and demographical data of ICU patients

Variables		Frequency n (%)
Age (year)	<40	24(19.05)
	40-50	16(12.70)
	50-60	25(19.84)
	60-70	28(22.22)
	≤70	33(26.19)
Gender	Male	73(57.94)
	Female	53(42.06)
Underlying disease	Blood disorders	12(9.52)
	Cancer	8(6.35)
	Kidney diseases	1(0.79)
	Post-surgery complications	49(38.89)
	Gastrointestinal diseases	20(15.87)
	Pulmonary diseases	10(7.94)
	Endocrine diseases	1(0.79)
	Diabetes	21(16.67)
	Other	4(3.17)
Number of days in ICU	One week	55(43.65)
	Two weeks	45(35.71)
	≤Three weeks	26(20.63)
Use of ventilator	Yes	79(62.70)
	No	47(37.30)
Need for vasopressor	Yes	29(23.02)
	No	97(76.98)
APACHE II score	10-14	17(13.49)
	15-19	33(26.19)
	20-24	42(33.33)
	25-29	28(22.22)
	30-34	6(4.76)
Patient's outcome	Discharged	87(69.05)
	Death	39(30.95)

Notably, the mean serum uric acid level in patients who died ($n=39$) was 4.99 ± 1.88 mg/dL, which was significantly higher than in discharged patients

Table 2. Demographical and clinical data according to the ICU patients' outcomes

Variables		Outcomes		p-value
		Discharge	Death	
Gender	Female	34(64.15)	19(35.85)	0.311*
	Male	53(72.60)	20(27.40)	
Underlying disease	Blood disorders	6(50.00)	6(50.0)	0.028**
	Cancer	4(50.00)	4(50.0)	
	Kidney diseases	0(0.00)	1(100)	
	Post-surgery complications	42(85.71)	7(14.29)	
	Gastrointestinal diseases	12(60.00)	8(40.00)	
	Pulmonary diseases	7(70.00)	3(30.00)	
	Endocrine diseases	1(100)	0(0.00)	
	Diabetes	12(57.14)	9(42.86)	
Use of ventilator	Yes	42(53.16)	37(46.84)	<0.001*
	No	45(95.74)	2(4.26)	
Need for vasopressor	Yes	8(27.59)	21(72.41)	<0.001*
	No	79(81.44)	18(18.56)	
APACHE II score	10-14	17(100)	0(0.00)	<0.001**
	15-19	33(100)	0(0.00)	
	20-24	31(73.81)	11(26.19)	
	25-29	6(21.43)	22(78.57)	
	30-34	0(0.00)	6(100)	
Age (year)	Mean±SD	56.97±16.11	55.33±19.07	0.810***
	Median (Q1, Q3)	59.00(43.00, 71.00)	59.00(46.00, 67.00)	
	Minimum-Maximum	24.00-85.00	18.00-83.00	
Creatinine level mg/dL	Mean±SD	0.97±0.19	0.98±0.20	0.773***
	Median (Q1, Q3)	0.97(0.80, 1.12)	1.00 (0.80, 1.12)	
	Minimum-Maximum	0.60-1.40	0.57-1.30	
Uric acid level mg/dL	Mean±SD	3.74±1.85	4.99±1.88	<0.001***
	Median (Q1, Q3)	3.30(2.40, 4.40)	5.10 (3.70, 5.90)	
	Minimum-Maximum	1.10-11.00	1.30-10.30	
Duration of ICU hospitalization	Mean±SD	9.29±6.74	14.41±11.43	0.024***
	Median (Q1, Q3)	8.00 (5.00, 12.00)	11.00 (6.00, 18.00)	
	Minimum-Maximum	2.00-45.00	2.00-45.00	

SD: Standard Deviation, Q: Quartile,

*Chi-square, **Fisher Exact test, ***Mann-Whitney U.

(n=87), who had a mean level of 3.74 ± 1.85 mg/dL ($p < 0.001$). Among the 39 deceased patients, 76.92% (n=30) had uric acid levels above the overall mean

value of 4.13 mg/dL, while only 40.23% (n=35) of discharged patients had levels above this mean, indicating a clear trend of higher uric acid levels in

fatal cases. Furthermore, logistic regression analysis confirmed that each 1 *mg/dL* increase in serum uric acid was associated with a 1.4-fold increase in the odds of death (OR: 1.37: 1.04–1.79; $p=0.022$) (Figure 1). The duration of ICU stay was also longer for deceased patients than those discharged ($p=0.024$) (Table 2).

Significant differences in uric acid levels between discharged and death outcomes were observed in patients aged 60 and above, with deceased patients showing higher levels of uric acid ($p<0.05$). Both female ($p=0.001$) and male ($p=0.041$) with death outcomes had significantly higher uric acid levels compared to the discharged patients (Figure 1). Patients requiring ventilators and those needing vasopressors for one week showed significantly higher uric acid levels with a higher rate of mortality ($p<0.001$) (Table 3).

The multivariate logistic regression analysis demonstrated that after adjusting for age, gender, underlying diseases, creatinine level, and days in ICU, significant associations were observed for using ventilator (OR:18.21, 3.80-87.08, 95%CI, $p<0.001$) and need for vasopressor (OR:9.15, 2.82-29.64, 95% CI, $p<0.001$), of which among ventilated patients and those who needed vasopressor, high chance of mortality was observed. The level of uric acid was significantly higher among patients with death outcome compared to discharged ones (OR:1.37, 1.04-1.79, 95%CI, $p=0.022$), of which by increasing one unit of serum uric acid, the odds of mortality increased by 1.4.

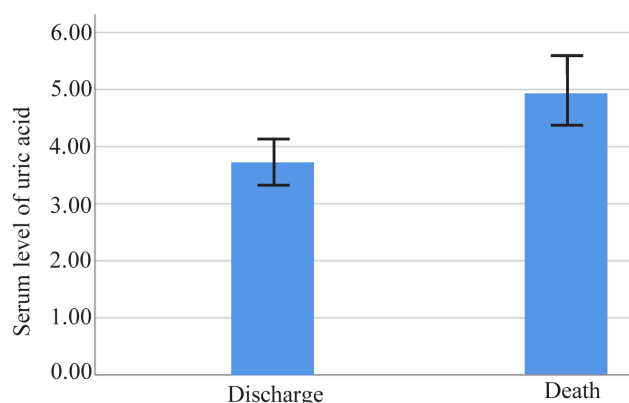


Figure 1. Comparison of mean serum uric acid levels on the first day of ICU admission in patients according to the outcomes.

Discussion

Evidence suggested that elevated uric acid levels could be associated with increased mortality risk in critically ill patients, possibly due to its impact on tissue oxygenation and organ function (23,24). The current study demonstrated significant differences in serum uric acid levels on the first day of admission between the two groups of outcomes. The findings indicated a significant association between uric acid levels and death outcomes among the ICU patients. The level of serum uric acid, especially at admission and during the early days of admission, strongly correlated with patient prognosis. Similar to the findings, a study by Pehlivanlar-Kucuk et al reported a significant difference in mean uric acid levels between non-survivors and survivors, with deceased patients exhibiting higher uric acid levels than those discharged (21).

Another study by Aminiahidashti *et al* demonstrated that elevated uric acid levels were associated with an increased mortality risk (25). Liu *et al* showed that mortality rates in ICU patients with sepsis increased dramatically with rising serum uric acid levels (26). In contrast, Zhu *et al* found no statistically significant relationship between serum uric acid levels and hospitalization outcomes or prognosis among patients with severe conditions (27). The complex interplay between uric acid metabolism, oxidative stress, and systemic inflammation in critically ill patients can lead to multi-organ dysfunction and increased mortality risk. In critically ill patients, hyperuricemia may exacerbate endothelial dysfunction, impair microcirculation, and contribute to organ damage. Moreover, elevated uric acid levels can lead to the formation of crystals in various tissues, potentially causing or worsening kidney injury, a common complication in ICU settings that can result in a higher mortality rate (28,29).

Findings of the current study showed that older patients had higher uric acid levels than others. Among patients over 60, the higher uric acid level significantly resulted in death outcomes. It was observed that women with hyperuricemia were more prone to death outcomes than men. Juraschek et al reported that uric acid level was associated with earlier mortality, especially in females (30). The greater vulnerability of women to death outcomes

Table 3. Comparison of serum uric acid levels in ICU patients with both outcomes (discharged or death) according to the uric acid level

Variables		Serum level of uric acid (mg/dL) Mean± SD/ Median (Q1, Q3)		p-value*
		Discharge	Death	
Age (year)	<40	3.13±1.62 3.00(2.15, 3.65)	4.29±1.65 4.70(3.25, 5.60)	0.061
	40-50	3.72±2.60 3.50(2.00, 4.70)	3.40±1.87 3.10(1.70, 5.40)	0.999
	50-60	4.46±1.94 4.20(3.05, 5.60)	5.30±2.71 5.00(3.60, 5.90)	0.452
	60-70	4.02±1.83 3.30(3.00, 4.10)	5.26±1.10 5.35(4.50, 5.90)	0.004
	≤70	3.47±1.36 3.10(2.35, 4.15)	5.52±1.75 5.20(4.70, 7.10)	0.003
Gender	Female	4.03±2.15 3.50(2.70, 4.40)	5.27±1.18 5.40(4.50, 5.90)	0.001
	Male	3.56±1.62 3.10(2.40, 4.30)	4.72±2.37 4.50(3.00, 5.85)	0.041
Days in ICU	One week	3.16±1.03 3.10(2.40, 3.70)	5.26±1.79 5.40(5.10, 5.90)	<0.001
	Two weeks	4.31±1.93 3.95(3.00, 4.90)	5.22±2.44 5.10(3.60, 5.90)	0.233
	≤Three weeks	4.14±3.06 2.75(2.30, 5.80)	5.45±1.48 4.60(3.70, 5.70)	0.131
Use of ventilator	Yes	3.45±1.98 3.05(2.30, 4.10)	4.96±1.92 5.10(3.70, 5.80)	<0.001
	No	3.93±1.72 3.50(2.90, 4.70)	5.50±0.57 5.50(5.10, 5.90)	0.118
Need for vasopressor	Yes	4.69±3.36 3.25(2.25, 7.00)	4.95±1.85 5.10(3.90, 5.80)	0.004
	No	3.65±1.63 3.30(2.40, 4.30)	5.03±10.97 5.15(3.60-6.40)	0.582
APACHE II score	10-14	2.95±0.99 3.00(2.40, 3.50)	-	-
	15-19	3.58±1.66 3.40(2.20, 4.20)	-	-
	20-24	4.34±2.26 3.70(2.70, 5.20)	3.90±1.56 4.30(2.60, 5.10)	0.933
	25-29	3.83±1.70 3.60(2.30, 5.10)	5.20±1.96 5.35(3.80, 5.80)	0.141
	30-34	-	6.18±1.10 5.90(5.20, 7.10)	-

SD: Standard Deviation, *Mann-Whitney U.

with hyperuricemia might be related to hormonal factors, differences in body composition, or variations in uric acid metabolism between genders (31). In another study by Guo *et al*, it was illustrated that in older adults, the uric acid level was associated with a higher mortality rate (32). Kikuchi *et al* found a high risk of mortality in both genders, patients with cardiovascular diseases, and those above 65 with hyperuricemia (33). The heightened mortality risk associated with hyperuricemia in individuals over 60 could be due to its potential role in exacerbating age-related conditions (34,35).

The current findings indicated that the frequency of death was significantly higher in ICU patients with diabetes, gastrointestinal diseases, and pulmonary diseases, respectively. A study by Xiong *et al* represented that patients with hyperuricemia and diabetes were more prone to chronic complications (36). Moreover, some gastrointestinal conditions can increase uric acid production or impair excretion. Shared risk factors, such as diet and metabolic disorders, further strengthen this association (37,38). Bartziokas *et al* stated that serum uric acid levels were linked to increased 30-day mortality in patients with respiratory diseases (39). Hyperuricemia also contributes to the development and progression of morbidity and mortality, including chronic kidney disease, metabolic disorders such as diabetes and obesity, and cardiovascular diseases (1,40).

The current study demonstrated that patients admitted for one week showed significantly higher uric acid levels among non-survivors than survivors. Patients with death outcomes were admitted in the ICU for more days than discharged ones. It was found that patients who used ventilators and needed vasopressors had higher levels of uric acid, and the frequency of death outcomes was higher among them than others. Although the use of vasopressors and ventilators is intended to reduce patient mortality, in the current study, patients requiring ventilators and vasopressors were often in life-threatening conditions, which inherently increases their mortality risk (41,42).

The results showed that ICU patients with first day APACHE II scores above 25 had higher levels of uric acid and were more susceptible to death outcomes. Patients with scores above 25 are typically critically ill with multiple organ dysfunctions. Tian

et al demonstrated that an APACHE score of 17 at third day is the best cut-off for defining patients at high mortality risk (22). In this state of severe physiological stress, the body may produce more uric acid due to increased cell death and tissue breakdown. The combination of severe illness (as indicated by high APACHE II scores) and elevated uric acid levels may synergistically contribute to a higher likelihood of mortality in ICU patients (20,43). According to current evidence, the first day remains the best time point for baseline APACHE II scoring, while the third day provides the most accurate prediction of mortality risk. In studies aiming to link biochemical markers such as uric acid to ICU outcomes, it may be beneficial to analyze levels in relation to both the baseline APACHE II score on day one and the more predictive day-three score to better understand how persistent physiological stress contributes to adverse outcome (22,44). However, this study's findings underscored the complex interplay of clinical factors in ICU patients' outcomes and highlighted the potential of uric acid as a prognostic marker; some limitations included the study's cross-sectional design that limited the ability to establish causal relationships and the small sample size from a single hospital might restrict the generalizability of the findings to broader populations or different healthcare settings. Moreover, the study accounted for no potential confounding factors such as specific treatments received during ICU stay or changes in uric acid levels over time, which could influence the observed associations and suggested to be considered in future studies.

Conclusion

The current study revealed significant associations between higher uric acid level, ventilator use, vasopressor requirement, and higher APACHE II scores that strongly linked to increased mortality risk. Notably, elevated uric acid levels emerged as a potential predictor of mortality in ICU patients. Moreover, demographic and clinical factors such as older age, female gender, and prolonged ICU stay were also correlated with an increased risk of death. These variables may reflect complex underlying physiological, hormonal, or care-related dynamics that warrant further investigation. The

multifactorial nature of ICU mortality highlighted in this study underlines the need for comprehensive risk assessments incorporating both laboratory and clinical parameters to improve patient management and outcomes.

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Ethics approval and consent to participate

All methods of this study were carried out following relevant guidelines and regulations. Written consent was obtained after informing each participant of the purpose and importance of the study, and for illiterate participants, informed consent was obtained from legal representatives. This study was approved by the Ethics Committee of Guilan University of Medical Sciences (IR.GUMS.REC.1399.591).

Declaration of generative AI in scientific writing

While preparing this work, AI was used to improve the manuscript's language and grammar. The author reviewed and edited the content as needed.

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Conflict of Interest

The authors declared no competing interests.

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