

## Association between Plasma Uric Acid Level and Mortality Rate in Children with Sepsis and Acute Kidney Injury

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**Purpose:** Acute kidney injury (AKI) is a common condition in hospitalized patients that can have a significant impact on outcomes, including an increase in overall complications and mortality rates. Criteria such as serum creatinine level, urinary output, and scoring systems such as KDIGO in acute conditions do not have acceptable specificity and sensitivity to evaluate kidney function. Therefore, this study was conducted to determine the relationship between plasma uric acid level and mortality rate in patients with sepsis and acute kidney failure.

**Materials and Methods:** In this descriptive-analytical (cross-sectional) study, 52 children aged from one month to 15 years with sepsis (based on qSOFA criteria) and acute kidney failure (based on serum creatinine level) admitted to the PICU of Ali Bin Abi Taleb Hospital from October 1401 to October 1402 were included and studied by the census method. Within 48 hours after admission to the ICU, blood samples were collected to check serum uric acid levels, electrolytes, albumin, complete blood count (CBC), kidney function tests, arterial blood gases, and chest x-rays. All patients were followed up until discharge or death due to progression of kidney failure. Finally, the findings of the research were analyzed using SPSS version 26 statistical software.

**Results:** The mean age of patients was  $3.66 \pm 4.92$  years. The number of deaths in the hyperuricemia group was significantly higher than in the normal uric acid group ( $P = 0.03$ ); an odds ratio of 3.45 indicates that a high level of uric acid is a risk factor for death. In this study, the duration of hospitalization was longer in those who survived ( $P = 0.02$ ). A particularly strong predictor in our analysis was the qSOFA score ( $P < 0.001$ ), highlighting its critical role in determining outcome. Serum uric acid level and qSOFA scale showed no significant difference overall ( $P = 0.76$ ); subgroup analysis among surviving and deceased patients between uric acid and the qSOFA scale presented the same result ( $P = 0.203$  and  $P = 0.29$ , respectively).

**Conclusion:** The level of uric acid can be considered a laboratory variable to predict the prognosis of patients.

**Keywords:** serum uric acid; kidney failure; sepsis; children

### INTRODUCTION

Sepsis is a systemic inflammatory response syndrome characterized by physiologic, pathologic, and biochemical abnormalities resulting from infection, which can impair organ function, ranging from organ dysfunction to septic shock with hypotensive shock, and cause multi-organ failure and serious complications. Currently, it affects about 10% of patients hospitalized in the ICU, and this index is increasing day by day. It has a significant impact on outcomes, including increased overall morbidity and mortality rates.<sup>(1)</sup> This injury causes functional decline and makes the patient severely ill, which is an important problem in critically

ill patients.<sup>(1)</sup> Acute kidney failure and sepsis are inseparably related and dependent in many patients. Sepsis is one of the causes of AKI, and AKI is one of the common complications of sepsis.<sup>(1)</sup> More than half of critically ill patients with AKI also have sepsis, and both are among the leading causes of mortality and complications in patients hospitalized in the ICU.<sup>(2,3)</sup> Sepsis-associated AKI (S-AKI) often results from tissue hypoperfusion, ischemia, and re-establishment of blood flow in the kidney, and is considered a type of pre-renal failure.<sup>(1)</sup> Since patients need time to receive medical care, if the disease has progressed extensively, it is difficult to prevent it. Therefore, screening high-risk patients and early diagnosis are necessary to provide supportive treatment

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**Table 1.** Comparison of demographic characteristics of participants

Variable	Categories	Alive (N=23)	Death (N=29)	P-value
Age (year), median (IQR)	2 (0.3–11)	0.5 (0.27–2)		0.61 <sup>a</sup>
BMI (kg/m <sup>2</sup> ), median (IQR)	15.6 (13.2–20.4)	14.32 (12.10–18.98)		0.37 <sup>a</sup>
Gender, Male, N (%)	12 (52.2%)	12 (41.4%)		0.48 <sup>b</sup>
Underlying disease, N (%)				---
	Neurological	6 (46.2%)	4 (33.3%)	
	Heart disease	3 (23.1%)	2 (16.7%)	
	Kidney	1 (7.7%)	0 (0%)	
	Hematological	0 (0%)	3 (25%)	
	Endocrine	0 (0%)	1 (8.3%)	

<sup>a</sup> Mann-Whitney U test; <sup>b</sup> Chi-square test. Abbreviations: IQR: interquartile range; BMI: Body Mass Index.

and avoid further complications. Uric acid is produced by liver cells, almost two-thirds of which are eliminated through the kidney and the rest through the digestive system. Several studies have proven the relationship between hyperuricemia and underlying systemic diseases such as chronic kidney disease (CKD), hypertension, diabetes, hyperinsulinemia, and cardiovascular diseases such as atherosclerosis.<sup>(4,5)</sup> Considering that uric acid has both oxidant and antioxidant properties, it can be effective in the sepsis process. The high level of oxyradicals and the lower amount of antioxidants in patients with sepsis lead to multi-organ failure. For this reason, measuring uric acid levels as an indicator of oxidative stress in patients with sepsis is helpful.<sup>(1)</sup> Based on the above, the present study was conducted to investigate the possible role of uric acid in predicting AKI and death in sepsis patients.

## MATERIALS AND METHODS

This cross-sectional, prospective, and descriptive-analytical study was conducted on all children between the ages of one month and 15 years with sepsis and acute kidney failure hospitalized in the PICU of Ali Ibn Abi Talib Zahedan Hospital over a one-year period from October 1401 to October 1402.

The definition and criteria of sepsis were based on the quick Sequential Organ Failure Assessment (qSOFA),<sup>(7)</sup> and AKI was defined as an increase in serum creatinine (sCr) of more than 0.3 mg/dL (or 26.5  $\mu$ mol/L) within 48 hours or an increase of sCr to 1.5 times the baseline serum creatinine within 7 days. Patients who met the mentioned criteria for sepsis and AKI were included in the study, and during their hospitalization in the ICU, their various characteristics such as age, gender, primary diagnosis of hospitalization, and underlying diseases were evaluated. Patients were also evaluated based on the uric acid level. According to age, uric acid was divided into two groups: hyperuricemia and normal uric acid level. The patient's vital signs were also recorded during admission (including pulse, respiration rate, blood pressure, and blood oxygen saturation). If the patient had chronic kidney failure before being admitted to the hospital, or if there was no relevant information on the amount of uric acid in the plasma within the first 24 hours of hospitalization, the patient was excluded

from the study. Within 48 hours after admission of patients to the ICU, blood samples were collected to check serum uric acid level, electrolytes, albumin, complete blood count (CBC), kidney function tests, and arterial blood gases, and chest radiographs were obtained. The reference time (time zero) for the survival analysis was determined as the time of admission to the Pediatric Intensive Care Unit (PICU). The main outcome was mortality in the PICU. Patients were monitored from admission to the PICU until they either died within the PICU or were discharged alive from the PICU (censoring). The follow-up did not extend beyond the PICU stay. All patients were followed up until discharge or death due to progression of kidney failure. This study was approved by the Medical Ethics Committee of Zahedan University of Medical Sciences (code: IR.ZAUMS.REC.1402.184).

## Statistical Analysis

Asymmetrically distributed variables are represented by median and interquartile range (IQR). The Kolmogorov-Smirnov test and visual inspection of Q-Q plots were used to investigate the condition of normal distribution of quantitative variables. Demographic and background variables were compared using the Mann-Whitney U test and the Chi-square test (with assessment of the assumptions). In addition, a comparative analysis of the characteristics of the disease was carried out. The Mann-Whitney U test and the Chi-square test were used for these comparisons. To demonstrate the strength of the difference between the variables, the effect size was calculated. Effect size was expressed as  $z/\sqrt{N}$  for the Mann-Whitney U test. The effect size,  $r$ , was interpreted as  $r \leq 0.3$  representing a small effect,  $0.3 < r < 0.5$  representing a medium effect, and  $0.5 \leq r$  representing a large effect. In addition, the odds ratio and 95% confidence interval were used to express the strength of the relationship using the Chi-square test. An odds ratio of less than 1 was interpreted as a lower probability of death in patients. In all comparison groups, the significance level was 0.05. IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, 2013), was used to perform the analysis. We utilized Kaplan–Meier survival analysis to compare mortality rates between the group with hyperuricemia and the group with normal serum uric acid levels. Cox

**Table 2.** Comparison of clinical condition based on life status (alive and death)

Variable	Categories	Total (N=52)	Alive (N=23)	Death (N=29)	P-value	Effect size
Hyperuricemia, N (%)		29 (55.8%)	9 (39.1%)	20 (69%)	0.03 <sup>a</sup>	3.45 (1.09–10.9) <sup>b</sup>
Duration of hospitalization (day), median (IQR)		10 (5–15)	12.5 (9.75–20.5)	8 (4.5–13)	0.02 <sup>c</sup>	-0.31 <sup>d</sup>
qSOFA, N (%)	1	8 (15.4%)	7 (30.4%)	1 (3.4%)	< 0.001 <sup>a</sup>	---
	2	21 (40.4%)	12 (52.2%)	9 (31%)		
	3	23 (44.2%)	4 (17.4%)	19 (65.5%)		

<sup>a</sup> Chi-square test; <sup>b</sup> odds ratio (95% confidence interval); <sup>c</sup> Mann-Whitney U test; <sup>d</sup> effect size measure for Mann-Whitney U analysis with  $r = z/\sqrt{N}$ .

**Abbreviations:** IQR: interquartile range.

**Table 3.** Comparison of survival time based on hyperuricemia state.

Hyperuricemia state	Mean (95% Confidence Interval)	Median (95% Confidence Interval)	Log Rank P-value
Without hyperuricemia	26.67 (18.83–34.50)	27.0 (18.23–35.76)	0.003
With hyperuricemia	12.77 (8.51–17.03)	8.0 (7.02–8.97)	
Total	18.59 (13.84–23.34)	20.0 (6.96–33.0)	

regression was utilized, after assessment of Cox Model Assumptions, to analyze the factors that contribute to mortality in patients diagnosed with sepsis and AKI in the pediatric intensive care unit; moreover, the assumptions of proportional hazards and linearity were confirmed. Variables for the multivariate Cox model were chosen based on clinical importance and existing literature knowledge, independent of their statistical significance in univariate analysis.

The sample size was calculated based on comparing mortality rates in septic children with hyperuricemia against those without it. Utilizing a two-independent proportion formula with the following parameters: frequency in the hyperuricemia group = 77.1%, frequency in the non-hyperuricemia group = 13.7%,  $\alpha = 0.05$ , and power = 80%, the required sample size was 8 patients per group (16 total).<sup>(5)</sup> The study was conducted over a one-year period, during which all eligible patients admitted to the PICU were enrolled (a consecutive sampling method). This resulted in a final sample size of 52 patients.

**RESULTS**

A total of 52 children who were hospitalized in the PICU (Pediatric Intensive Care Unit) ward because of sepsis and acute kidney injury were enrolled. The mean age of patients was  $3.66 \pm 4.92$  years, with a minimum of 1 and a maximum of 15 years. Thirty-five (67.3%) of the patients were under 2 years old, 8 (14.14%) were between 2 and 10 years old, and 9 (16.3%) were between 10 and 18 years old. Twenty-four (46.2%) of the patients were male. The mean BMI in total participants was  $15.96 \pm 4.56$ . There was no statistically significant difference in age and BMI between the two groups of patients with different prognoses for survival ( $P = 0.61$  and  $P = 0.37$ , respectively). The distribution of underlying disease is also presented in **Table 1**.

The number of deaths in the hyperuricemia group was significantly higher than in the normal uric acid group ( $P = 0.03$ ); an odds ratio of 3.45 indicates that a high level of uric acid is a risk factor for death. In this study, the duration of hospitalization was longer in those who survived ( $P = 0.02$ ).

The frequency of the qSOFA scale indicates a statistical difference based on the outcome (alive or dead) ( $P < 0.001$ ) (**Table 2**). Serum uric acid level and qSOFA scale showed no significant difference in total ( $P = 0.76$ ); subgroup analysis of surviving and deceased patients between uric acid and the qSOFA scale presented the same result ( $P = 0.203$  and  $P = 0.29$ , respec-

tively) (**Figure 1**). Finally, survival analysis with the Kaplan-Meier test presented mean and median survival times. The median survival time in patients without hyperuricemia was 27.0 (18.23–35.76), while the median in the hyperuricemia group was 8.0 (7.02–8.97); the log-rank P value was statistically significant ( $P = 0.003$ ). The details are shown in **Figure 2 and Table 3**. Finally, the Cox regression model with backward (conditional) selection was used to assess prognostic risk factors associated with mortality. Hyperuricemia, age, BMI, qSOFA score, and gender variables were entered into Cox regression analysis. Based on the final reliable model ( $P = 0.002$ ), hyperuricemia and female gender were statistically significant risk factors for patient mortality ( $P = 0.0093$ , HR (95% CI): 3.33 (1.37–8.33); and  $P = 0.03$ , HR (95% CI): 2.50 (1.06–5.88), respectively) (**Table 4**).

**DISCUSSION**

Sepsis is a significant burden in ICUs worldwide, and its incidence is increasing every year. AKI is a common complication of sepsis with an incidence of 40–50%.<sup>(6–10)</sup> AKI increases the length of hospital stay, medical costs, and risk of death in patients with sepsis, and it increases the risk of long-term CKD or even end-stage renal disease.<sup>(11–14)</sup> Early identification and intervention of risk factors for sepsis-related AKI are essential to reduce the risk of AKI. In recent years, the number of risk factors for sepsis-related AKI has increased, and uric acid has been considered a risk factor for the onset and progression of CKD and AKI.<sup>(15,16)</sup>

Criteria such as serum creatinine level, urinary output, and scoring systems such as KDIGO in acute conditions do not have acceptable specificity and sensitivity to evaluate kidney function;<sup>(5)</sup> therefore, in this study, the relationship between plasma uric acid level and mortality rate in patients with sepsis and acute kidney failure was investigated. The results of our study showed that the occurrence of death had a significant relationship with hyperuricemia ( $P = 0.031$ , OR = 3.45) and the severity of sepsis. In their study, Chen et al. observed that children with hyperuricemia had a higher mortality rate (50% vs. 10%) compared to those with normal uric acid levels. However, these patients were more hemodynamically unstable than the surviving patients.<sup>(17)</sup> Woolliscroft et al. compared the rate of uric acid excretion and serum uric acid in patients with acute cardiovascular disease and showed that patients with higher uric acid levels and lower uric acid excretion had a higher mortality rate. These cases also

**Table 4.** Association factors with survival time: results of Cox regression analysis.

Variables	B	Significance	Hazard Ratio (95% CI)
Hyperuricemia (with/without)	-1.19	0.02	3.33 (1.37–8.33)
Gender (female/male)	0.89	0.037	2.50 (1.06–5.88)

**Abbreviation:** CI: confidence interval.

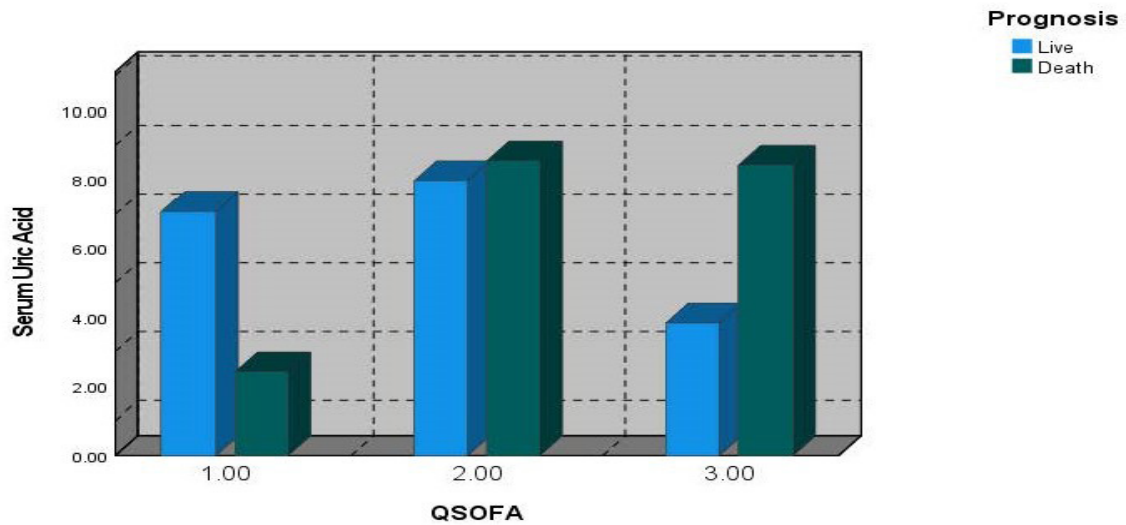


Figure 1. Serum uric acid level at different stages of qSOFA based on prognosis.

had lower blood pressure and worse blood circulation.<sup>(18)</sup> Furthermore, infants who underwent cardiac surgery and had very high serum uric acid levels either developed anuric acute renal failure or died.<sup>(19,20)</sup> Hooman et al. (2010, Iran) investigated the diagnostic value of uric acid as a predictor of mortality in critically ill children. In this prospective cohort study, 220 children (96 girls and 124 boys) who were admitted to the pediatric intensive care unit for at least 24 hours were examined. Serum uric acid level was measured on the first day of

PICU admission, and death or transfer from PICU was considered as the outcome. The findings of this research showed that out of 44 patients whose serum uric acid level was more than 8 mg/dL, 17 died, which was associated with a higher relative risk of 1.88 and higher mortality ( $P < 0.05$ ). The relative risk of death in patients who had serum uric acid  $> 8$  mg/dL and needed vasopressors was 1.04, and in patients under mechanical ventilation it was 1.33. In patients with a children's mortality risk higher than 38 points, it was

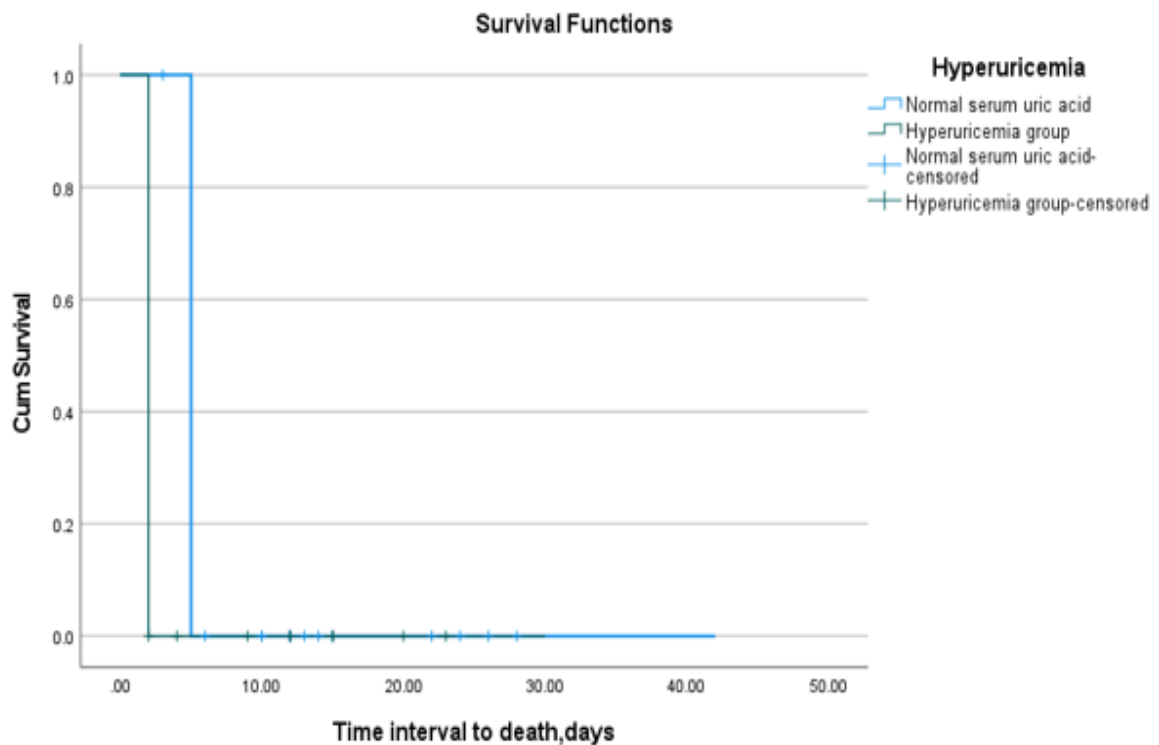


Figure 2. Comparison of survival time between patients with and without hyperuricemia; Kaplan-Meier analysis, log-rank test.

1.4, and in septic cases, it was 4 ( $P < 0.05$ ). Therefore, they concluded that uric acid level on the first day of intensive care admission is not an independent risk factor for mortality in the PICU. However, the need for mechanical ventilation or inotropic agents was associated with a poor outcome, and only higher uric acid levels in sepsis had an increased risk factor;<sup>(6)</sup> the findings of this research are consistent with our study in terms of the predictive value of uric acid level in sepsis on the results of treatment.<sup>(21)</sup> Among the strengths of this research were the larger sample size compared to the current study and the examination of a combination of events such as hypovolemia, sepsis, drug nephrotoxicity, hemodynamic instability, severity of the underlying disease, and hospital-acquired infections in the prognosis of patients. However, it seems that the sampling in the present study was done more carefully, and the role of other factors such as hypovolemia, nephrotoxicity, etc., was controlled as much as possible. In another study conducted by Jiang et al. (2023, China) to investigate the relationship between hyperuricemia and acute kidney injury in critically ill patients with sepsis hospitalized in the ICU, it was shown that the incidence of AKI in the groups with and without hyperuricemia was 76.7% and 42.3%, respectively, which were statistically significant differences. After adjusting for gender, comorbidities (coronary artery disease), organ failure assessment, SOFA score on the day of admission, baseline renal function, serum lactate, procalcitonin, and mean arterial pressure, hyperuricemia was found to be an independent risk factor for AKI following sepsis (OR = 4.415, 95% CI 2.793–6.980,  $P < 0.001$ ), and for every 1 mg/dL increase in serum uric acid, the risk of AKI increased by 31.7%. Therefore, they concluded that AKI is a common complication in septic patients hospitalized in the ICU and that hyperuricemia is an independent risk factor for AKI in septic patients. The findings of this research are also consistent with our study in terms of the relationship between hyperuricemia and mortality. However, one of the weak points of both studies is the lack of examination of changes in the serum creatinine level and its comparison with the baseline creatinine level and urinary output level. Therefore, it is suggested that in future research, a case-control study should be conducted to investigate the uric acid level by matching for age, gender, and underlying diseases, to measure the sensitivity and specificity of uric acid in predicting treatment prognosis using ROC curve analysis.<sup>(22)</sup> The study of Li et al. (2023, China), aimed at the relationship between serum uric acid level and clinical outcomes in patients with acute kidney injury, showed that in multivariate analysis, after adjusting for various confounding factors in the fully adjusted model, a higher serum uric acid level was associated with increased in-hospital mortality in AKI patients with an odds ratio of 1.72. ROC curve analysis also showed that a serum uric acid level above 6.9 mg/dL was associated with 51% sensitivity and 73% specificity for predicting mortality risk. Therefore, they concluded that the serum uric acid level can be considered as a marker to check the prognosis of these patients. Thus, it can be stated that, epidemiologically, uric acid has acceptable predictive power for AKI; however, the low sensitivity of this laboratory variable can cause its non-acceptance at the clinical level. In addition, Li et al.'s study was conducted at the population level with an age range of over

18 years; therefore, conducting standard studies in the pediatric age range to investigate the predictive power of uric acid seems mandatory.<sup>(23)</sup>

A combination of multifactorial events such as hypovolemia, sepsis, drug nephrotoxicity, hemodynamic instability, the severity of the underlying disease and its complications, and nosocomial infections may affect the outcome of patients admitted to the PICU. Therefore, what happens in the following days may be as important as the initial condition of the patients. We suggest that measurement of serum uric acid by recording all changes during the entire hospitalization period may predict patient prognosis better than a single measurement on the first day of admission, which was one of the current limitations. Also, even though we selected confounders for our multivariable model using robust clinical reasoning and existing literature, residual confounding from unmeasured or inaccurately measured factors remains possible. The limited sample size ( $N = 52$ ) might influence the generalizability of our results. Additionally, the comparatively small sample size ( $N = 52$ ) could influence the generalizability of our results. Consequently, our findings, especially the non-significant ones, must be viewed carefully and need to be verified in larger cohort studies.

## CONCLUSIONS

AKI, as a common side effect of life-threatening events such as sepsis, trauma, etc., has always been a concern of physicians. By reducing the clearance of toxic substances produced in the body, it causes a decrease in the level of consciousness and prevents invasive procedures. Therefore, identifying reliable variables that reveal AKI as soon as possible can help in the management of these patients. This becomes more important in pediatrics due to the more unstable conditions of these patients. Finally, it can be stated that the level of uric acid can be considered a laboratory variable to predict the prognosis of these patients.

## SUMMARY

Hyperuricemia is significantly associated with higher mortality in children with sepsis and acute kidney injury, and may serve as a useful laboratory predictor of prognosis.

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