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The Effect of Hyperuricemia On Acute Renal Failure Due To Sepsis In Elderly Intensive Care Patients and The Relationship With Cancer

Hasan Açık[1], Gülen Açık[2], Kağan Gökçe[3*]

[1]Istanbul Okan University, Faculty of Medicine, Department of Internal Medicine, İstanbul, Türkiye
[2]Istanbul Okan University, Faculty of Medicine, Department of Anesthesiology and Reanimation, İstanbul, Türkiye
[3]Istanbul Okan University, Faculty of Medicine, Department of General Surgery, Surgical Oncology, İstanbul, Türkiye

ABSTRACT

The aim of our study is to assess hyperuricemia as an early biomarker of sepsis-related acute kidney injury and mortality in elderly cancer patients.

This retrospective study was conducted on patients with sepsis, who were hospitalized in the intensive care unit (ICU), based on the quick Sequential Organ Failure Assessment (qSOFA) score. Patients were categorized into two groups depending on their uric acid levels. The first group had a serum uric acid level of ≥7 mg/dL, whereas the second group had a serum uric acid level of <7 mg/dL.

The median age was 73.5 years, ranging from 65 to 82 years. Among the 106 patients, 35 patients had hyperuricemia. Acute kidney injury was developed at a statistically significantly higher rate in the group of patients with hyperuricemia than in the group of patients with normal uric acid levels (p=0.019). However, mortality rates were found to be similar in both groups. According to the statistics, the group with hyperuricemia had a significantly longer length of stay in the ICU (P=0.019). Multiple models revealed that having malignancy (p=0.003; OR:5.771) and a high qSOFA score (p=0.0001; OR:5.535) were risk factors that increased the risk of mortality.

The rates of AKI development were found to be statistically significantly higher in the hyperuricemic group. The risk of mortality in elderly hyperuricemic cancer patients hospitalized in the ICU is higher than in non-hyperuricemic patients. Hyperuricemia can be used as one of the early biomarkers of sepsis-related AKI.

Keywords: Hyperuricemia, acute renal failure, sepsis, cancer, intensive care

Introduction

Hyperuricemia is frequently observed in elderly cancer patients due to chemotherapy treatments and comorbidities such as hypertension (1). Tumor Lysis Syndrome and hyperuricemia may occur due to the cytotoxic effect of radiotherapy, chemotherapy, and immunotherapy (2). More than half of newly diagnosed cancer patients are elderly patients aged 65 and over. Two-thirds of cancer-related deaths occur in this group of patients (3). There is a positive and independent relationship between the decrease in muscle mass and hyperuricemia, especially due to cachexia, in older age. Hyperuricemia is likely to occur, especially in malignancy patients who are elderly, cachectic, and have comorbidities such as hypertension, considering the oncological treatments they have previously received (4,5).

Uric acid, which is the final product of purine metabolism, is excreted from the body primarily through the kidneys and also through the intestinal system. Urate is filtered in the glomeruli and then absorbed by the proximal tubules of the kidney (6,7). Considering previous nephrotoxic chemotherapy and immunotherapy treatments, the possibility of developing acute kidney injury is quite high in late-stage cancer patients with high uric acid levels and sepsis (8-11). The serum uric acid concentration level is determined by factors such as increased production, decrease in glomerular filtration rate, insufficient blood supply to the kidney, increase in tubular reabsorption, and decrease in excretion (12-14). Although the complete mechanism is not fully understood, studies showed that uric acid exacerbates oxidative stress and inflammation by stimulating nicotinamide adenine dinucleotide phosphate

***Corresponding Author:** Kağan Gökçe, İçmeler Mahallesi, Aydınlı Yolu Caddesi, Okan Üniversitesi Tıp Fakültesi Araştırma ve Uygulama Hastanesi, Genel Cerrahi Anabilim Dalı, No: 2, 34947 Tuzla, İstanbul, Türkiye
E-mail: kgngkc@hotmail.com, Phone: +90 532 581 05 90
ORCID ID: Hasan Açık: 0000-0002-7247-8164, **Gülen Açık:** 0000-0003-4723-6523, **Kağan Gökçe:** 0000-0003-4712-0512
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oxidase, thromboxane, and cyclooxygenase-2 activity, resulting in glomerular hypertension and fibrosis (15,16). Furthermore, uric acid increases oxidative stress by stimulating plasma renin activity and expression. In addition, uric acid crystals obstruct renal tubules and cause Acute Kidney Injury (AKI) (9,15,16). There are some classifications for defining and stratifying AKI. Kidney Disease Improving Global Outcomes (KDIGO) classification is commonly used to diagnose AKI. This classification categorizes patients into three stages; as first 0.3 mg/dL increase in serum creatinine level within 48 hours, as second 1.5-fold increase in serum creatinine level at the baseline, as third a decrease in urine output <0.5 mL/kg/h throughout 6 hours (11,17).

Sepsis, which is an important cause of morbidity and mortality in Intensive Care Unit (ICU), is associated with organ dysfunction, such as AKI, and constitutes the majority of the reasons for admission to the ICU. Therefore, early diagnosis is important, and treatment of sepsis must be well known. The quick Sequential Organ Failure Assessment (qSOFA) score was approved for fast decision-making. This score includes three criteria first of them is Glasgow Coma Scale (GCS) ≤14, second is systolic blood pressure ≤100 mmHg, and third is respiratory rate ≥ 22 breaths/min. Due to its simplicity, the qSOFA scale is recommended (18). There are many studies conducted to find early biomarkers easily to prevent sepsis-related mortality and AKI development (9,14,15). Laboratory tests can determine uric acid levels. Elevated uric acid levels can be used in the early detection of patients at high risk of developing AKI and mortality (19,20).

In our literature review, we found that while the impact of hyperuricemia on morbidity and mortality among intensive care patients has been investigated, there is a lack of sufficient studies focusing on end-stage patients. Our research can provide valuable insights into this topic and contribute to the existing body of literature. We hypothesized that uric acid can be considered as one of the sepsis biomarkers. In this study, we aimed to assess hyperuricemia as an early biomarker of sepsis related AKI and mortality.

Materials and Methods

This retrospective study was structured by examining patients in the intensive care unit between January 2021 and May 2023. Patients' data were collected from files and the hospital's electronic system. All the patients, who were older than 65 and diagnosed with sepsis according to qSOFA score in ICU, were included. Patients, who had chronic renal failure, AKI on admission to the ICU, a history of drug use that affected their uric acid levels, and a hospitalization period in the ICU that was less than 24 hours or longer than two months, were excluded.

Patients' data; Age, gender, comorbidities, stay time in ICU, cause of sepsis, and etc. were all noted. The comorbidities included Chronic Obstructive Pulmonary Disease (COPD), Diabetes Mellitus (DM), Coronary Artery Disease (CAD), Hypertension (HT), and malignancy. Vital signs, qSOFA, and Acute Physiology Health Disease Classification System II (APACHE II) scores at admission and mortality rates were recorded. Blood samples were obtained in the first day in the ICU. Serum uric acid, creatinine, urea, C-Reactive Protein (CRP), procalcitonin, and blood count levels were recorded. We defined hyperuricemia using a uric acid saturation cutoff of 7 mg/dL, consistent with the threshold used in most other studies for both males and females, as all women in this study were post-menopausal. The duration of mechanical ventilation of the patients and the length of stay in ICU was documented. Patients were divided into two groups; First was the normal serum uric acid <7 mg/dL group, and the second was hyperuricemia ≥7 mg/dL group. Moreover, AKI was defined using KDIGO guidelines.

Statistical Analysis: All statistical analyses were performed using SPSS 25.0 (IBM SPSS Statistics 25 software (Armonk, NY: IBM Corp.)). Continuous variables were defined by the median (IQR: 25th and 75th percentiles) and categorical variables were described by number and percent. Shapiro Wilk and Kolmogorov Smirnov tests were used to describe normal distribution. If parametric test conditions were satisfied, an independent samples t-test was used, if parametric test conditions were insufficient, the Mann-Whitney U-test was used for comparison between groups The Chi-Square test was used for categorical variables. Univariate and multiple logistic regression models were used to determine the mortality risk factors. Statistical significance was $p \leq 0.05$.

Results

145 patients were recruited into the study. 21 patients were excluded due to chronic renal failure, 12 patients were excluded due to AKI on admission to the ICU, and six patients were

Table 1: The Comparison of Clinical Data

	Uric acid <7 g/dL	Uric acid ≥7 g/dL	P value
Age, yr, med (IQR)	75 (63-84)	70 (62-79)	0.196 b
Gender			
Female, n (%)	33 (46.5)	15 (42.9)	0.725 a
Male, n (%)	38 (53.5)	20 (57.1)	
Comorbidities			
DM, n (%)	38 (53.5)	21 (60)	0.825 a
HT, n (%)	38(53.5)	21(60)	0.528 a
CAD, n (%)	14(19.7)	12(34.3)	0.101 a
COPD, n (%)	15 (21.1)	10 (28.6)	0.396 a
Malignancy, n (%)	21(29.6)	16 (45.7)	0.101 a
qSOFA			
2, n (%)	38 (53.5)	15 (42.9)	0.302 a
3, n (%)	33 (46.5)	20 (57.1)	
AKI, n (%)	20 (28,2)	18 (51,4)	0.019 a

*p<0.05 statistically significant; Med (IQR): Median (25th – 75th percentiles); a: Chi-Square test; b: Mann Whitney U test. DM: diabetes mellitus, HT: hypertension, CAD: coronary artery disease, COPD: chronic obstructive pulmonary disease, qSOFA: quick Sequential Organ Failure Assessment, AKI: acute kidney injury

Table 2: Comparison of ICU Data Between The Two Groups

	Uric acid <7 g/dL	Uric acid ≥7 g/dL	P value
Duration of MV, d, Med (IQR)	5 (2 - 13)	5 (2 - 11)	0.578 b
ICU stay, d, Med (IQR)	9 (4 - 13)	12 (7 - 21)	0.019 b
Hospital mortality, n (%)	46 (64.8)	22 (62.9)	0.845 a

*p<0.05 statistically significant; Med (IQR): Median (25th – 75th percentiles); a: Chi-Square test; b: Mann Whitney U test. MV: mechanical ventilation, ICU: intensive care unit.

excluded due to their hospitalization period in the ICU, which was less than 24 hours or longer than two months. 48 females, 58 males a total of 106 patients were included in the study. The median age was 73.5 years, ranging from 65 to 82 years. Of 106 patients 41% had DM, 55% had HT, 24% had CAD, 23% had COPD and 35% had malignancy. The qSOFA score was two for 53 patients and three for 53 patients. The median APACHE score of all patients was between 19 and 28; and an average of 24 (19-28). Of all patients, who were included in the study, had sepsis due to pneumonia (75%), urinary tract (17%), intra-abdominal (6%), mediastinal (1%), and catheter (1%).

Patients were divided into a normal serum uric acid level group (n=71, 67%) and a hyperuricemia group (n=35, 33%). There was no significant statistical difference in age and gender between the two groups (Table 1).

According to the results, no significant difference was found when the duration of mechanical ventilation was compared in both groups (Table 2). When the length of stay values between the two groups were compared, it was observed that patients in the hyperuricemia group had statistically significantly higher values (p=0.019).

Of 106 patients, AKI developed in 38 (35.8%) patients. This rate was 51.4% in the hyperuricemia group and 28.2% in the normal uric acid group. This situation was considered statistically significant (p=0.019) (Table 1). According to the KDIGO classification system, three patients, that developed AKI were evaluated as stage one, 10 patients as stage two, and 25 patients as stage three.

No statistically significant difference was found when the mortality rates between the two groups were compared. Mortality was 62.9% in the hyperuricemia group, meanwhile, it was 64.8% in the normal uric acid group (p=0.845) (Table 2).

The risk factors that affect mortality were analyzed using the logistic regression method. The risk factors with univariate models were analyzed and then considered with multiple models where

they were significant. After conducting univariate analysis, we found that the presence of malignancy (p=0.001; OR:5.867) and a high qSOFA score (p=0.0001; OR:4.816) were factors that increased the risk of mortality. After further analysis of significant factors, the multiple models revealed that having malignancy (p=0.003; OR:5.771) and a high qSOFA score (p=0.0001; OR:5.535) were risk factors that increased the risk of mortality.

Discussion

Morbidity and mortality rates are higher in CAD and cancer patients with high uric acid levels than in other groups of patients. Long-term mortality rates are higher in elderly patients with chronic heart disease and high uric acid levels than in patients with normal uric acid levels. High uric acid levels in the acute phase can be considered a predictive factor for mortality (21). Patients with leukemia, lymphoma, ovarian, liver, kidney, and all other cancers, especially multiple myeloma, have a higher risk of kidney damage requiring replacement therapy. In addition, cancer is an independent risk factor for all-cause mortality. In our study, we found that hyperuricemic cancer patients in ICU had a statistically higher risk of mortality than the non-hyperuricemic group. AKI that would require replacement therapy is important in terms of morbidity and mortality in all other cancer patients, especially in multiple myeloma. Considering the possible kidney damage in sepsis and malignancy patients, it is important to evaluate patients in terms of mortality and morbidity (22).

Hyperuricemia is the potential risk factor for AKI in patients with sepsis (23,24). Serum uric acid level of 6.9 mg/dL increases the need for mechanical ventilation in intensive care patients with respiratory disease and prolongs the length of stay. Uric acid, which is a low-cost test, has a great role in predicting the development of AKI and mortality in patients with sepsis. The cut-off value of uric acid for the risk of developing AKI was determined as 7.25 mg/dL (15,25). However, a meta-analysis conducted with a high number of patients showed that hyperuricemia did not affect mortality in patients with sepsis. The effect of hyperuricemia on mortality was investigated by comparing the uric acid levels of patients who died and survived in the ICU and no significant association between hyperuricemia and long-term mortality was found (15,26).

In our study, we found that high uric acid levels did not make a difference in long-term mortality. When we compared the duration of mechanical ventilation between the two groups with high and normal uric acid levels, we found that there was no statistical significance. There are not many studies on hyperuricemia and the duration of mechanical ventilation. Hyperuricemia may be a risk factor for the development of acute respiratory distress syndrome, but a clear correlation has not been shown. Uric acid elevation was investigated in elective cardiovascular surgery patients, it was observed that the duration of mechanical ventilation was significantly longer in the hyperuricemia group (27).

In our study, the length of stay in the ICU was significantly longer in the hyperuricemia group than in the normal uric acid group. Hyperuricemia increased the risk of developing AKI and patients with AKI had longer stays in the ICU, which was associated with poor prognosis (28). Patients with hyperuricemia were more likely to stay in the ICU by the end of 72 hours. Thus, it is thought that uric acid can be an indicator of disease severity, such as in APACHE II score, and can be used to predict the length of stay in the ICU (29). The mortality rate was 63.6% in patients with a qSOFA score of three, meanwhile was 36.8% in those with a qSOFA score of two. Our data is consistent with a study, in which mortality rates were compared to patients with a qSOFA score of two and three. It was significantly higher in patients with a qSOFA score of three (19).

Even asymptomatic hyperuricemia (≥6.8 mg/dL) is a risk factor for resistant hypertension in patients >65 years. Weakening of skeletal muscles in older patients is a risk factor for hyperuricemia. Muscle loss and hyperuricemia due to malnutrition in elderly cancer patients are significant in terms of prolonged intensive care unit stays, morbidity, and mortality. In our study hyperuricemia was a statistically independent risk factor for mortality in cancer patients in ICU (4,30).

Many markers can be used as sepsis biomarkers and uric acid can be considered as one of them. The present research indicates that uric acid levels could serve as an early indicator of the severity of sepsis and the risk of developing AKI. Uric acid levels can be used to predict the prognosis of the disease, as in the APACHE II scoring system. This may enable us to reduce mortality by detecting the development of AKI early, which is one of the biggest causes of mortality in sepsis. The results of our study show that hyperuricemia can be an early biomarker of sepsis-related AKI. The rates of AKI development were statistically

higher in the hyperuricemic group. Mortality risk in elderly hyperuricemic cancer patients hospitalized in ICU is higher than in non-hyperuricemic patients.

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