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ORIGINAL ARTICLE

The Association Between Serum Uric Acid Level and Prognosis in Critically Ill Patients, Uric Acid as a Prognosis Predictor

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SUMMARY

Background: **Uric acid is synthesized from xanthine via xanthine oxidase as an end-product of purine metabolism. Uric acid is a major non-enzymatic antioxidant in the blood, and it exerts a protective action on vitamin C. There are a limited number of ICU studies related to uric acid, which is a valuable prognostic biomarker. This study aimed to evaluate the utility of uric acid as a biomarker in predicting the outcomes of critically ill patients.**
Methods: **This prospective, multi-centered cohort study included 128 patients from two different intensive care units who met the study inclusion criteria between May 2017 and October 2017. Study inclusion criteria were first admission to the ICU, age > 18 years, and ICU stay > 24 hours. In each patient, baseline serum uric acid levels were measured after acute interventions, prior to the initiation of the treatment process.**
Results: **When comparing the last uric acid levels of patients, the median last uric acid levels in the non-survival and survival groups were significantly different (p = 0.001). A last uric acid level > 4.5 mg/dL was associated with a 2.638 times higher risk (relative risk) for mortality. According to ROC analysis, a cutoff value of 1.5 for the ratio between the last two uric acid levels had a sensitivity of 0.21 and a specificity of 0.96 for predicting mortality. A 1.5-fold increase in the uric acid level yielded a positive predictive value of 92.6% and a negative predictive value of 65.2% for predicting mortality. The median uric level in the patient subset with ARDS, was significantly higher than those without ARDS (p = 0.001).**
Conclusions: **Results of this study indicate that a time-dependent increase in uric acid levels can be used as an important biomarker for predicting mortality in critically ill patients; further, uric acid levels should possibly be included in the current mortality risk scoring systems. In addition, elevation of uric acid, a simple, inexpensive, and readily available biomarker, may provide guidance in the diagnostic stage and in predicting clinical outcomes of patients with sepsis or ARDS.**
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INTRODUCTION

Uric acid is synthesized from xanthine via xanthine oxidase as an end-product of purine metabolism [1]. Elevated uric acid levels may be caused by an increased production of urate or by a reduction in renal uric acid excretion, or both [2]. The kidneys are responsible for the majority of daily uric acid excretion. More than 90%

of all hyperuricemia cases are due to disturbances in uric acid excretion. Uric acid crystals can adhere to the surface of renal epithelial cells, which reduces the glomerular filtration rate. Increased uric acid levels can result in the development of both systolic and glomerular hypertension, which are associated with increased renal vascular resistance and reduced renal blood flow [3]. Uric acid levels vary between males and females. Normal uric acid levels are generally defined as > 6.5 mg/dL (390 μmol/L) or 7 mg/dL (420 μmol/L) for men, and > 6 mg/dL (360 μmol/L) for women [4]. Although the pathophysiological mechanisms remain unclear, serum uric acid levels have been associated with endothelial dysfunction, antiproliferative action, and increased oxidative stress [5,6]. At low serum levels, uric acid has antioxidant properties, but a pro-oxidant state is observed when levels are elevated [5,7]. Uric acid is a major non-enzymatic antioxidant in the blood, and it exerts a protective action on vitamin C, which is an indicator of oxidation state in organisms [8]. In one study, elevated serum uric acid levels were associated with the severity of coronary artery disease in non-diabetic and non-hypertensive patients with acute coronary syndrome [9]. In addition, it has been reported that this low-cost biomarker can be useful in identifying high risk patients with chronic obstructive lung disease that are likely to benefit from treatment [10]. Further, some studies have shown that elevated blood uric acid levels are associated with systemic inflammation and hypoxia [11,12]. Similarly, publications have shown that changes in the oxygen carrying parameters as well as hypoxanthine, xanthine, and blood uric acid concentrations can be used in evaluating microcirculation [13]. Microcirculatory changes play an important role in critically ill patients. There are a limited number of ICU studies related with uric acid, which is a valuable prognostic biomarker. Since critically ill patients are treated in the ICU, prognostic predictors for these patients are extremely valuable. In one study conducted in an adult ICU, uric acid levels measured on the first day of ICU admission were not associated with mortality; however, they were associated with mechanical ventilation requirement [14]. Patients with sepsis or ARDS constitute an important part of ICU admissions, and previous studies have shown that serum uric acid level is associated with disease severity and prognosis in these patients [15,16].

The present study aimed to evaluate the utility of uric acid level as a biomarker for predicting the outcomes of critically ill patients admitted to the ICU. The primary outcome of the study is the association of serum uric acid levels measured at admission with all-cause mortality at the end of the 7th, 28th, and 60th days. The secondary outcome is the association of serum uric acid levels with clinical diagnosis such as ARDS and sepsis, and the scoring systems that are used to predict organ failure and mortality in the ICU.

MATERIALS AND METHODS

Study group

This study is a multi-centered, prospective cohort study conducted in the General ICU of our University, Faculty of Medicine and in the Anesthesiology and Reanimation ICU of State Hospital. The local ethics committee reviewed and approved the study protocol prior to the start of the investigation (2017/178). Included study patients were admitted to either of the two ICUs defined above between May 2017 and October 2017. Study inclusion criteria were first admission to the ICU, age > 18 years, and ICU stay > 24 hours. Study exclusion criteria were age < 18 years, chronic dialysis, acute renal failure with creatinine level > 3 mg/dL, pulmonary hypertension, allopurinol treatment, chronic liver failure, pregnancy, and renal trauma. Seventeen of the total 145 patients were not included in the study: 3 were < 18 years old, 4 were undergoing chronic dialysis, 6 had creatinine levels > 3 mg/dL following acute renal failure (ARF), 2 had chronic liver failure, and 2 had pulmonary hypertension. The study included 128 patients who met the study criteria.

Patient data

In each patient, baseline serum uric acid levels were measured after acute interventions, prior to the initiation of the treatment process. Serum uric acid levels were measured with the uricase colorimetric (enzymatic color test) assay. The assigned uric acid reference ranges in the institutions were 3.5 - 7.2 mg/dL for males and 2.6 - 6.0 mg/dL for females. After measuring the baseline levels at admission, serum uric acid levels were measured once every three days of ICU stay. For patients with prolonged ICU stay, the maximum uric acid follow-up time was defined as 60 days.

Additionally, the patients' demographic data, primary admission diagnoses, comorbidities, Acute Physiology and Chronic Health Evaluation (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores (assessed within 24 hours of admission), vital signs (pulse rate, systolic/diastolic blood pressure, body temperature), and biochemical parameters (hemoglobin, blood gas, lactate, Na, K, Mg, BUN, creatinine, albumin, ALT, AST, CRP) were recorded. Patients were assessed for the presence/absence of ARDS and sepsis at the time of admission and during their ICU stay. A diagnosis of ARDS was made according to Berlin criteria [17], and a diagnosis of sepsis was made according to the 2016 sepsis/septic shock guidelines [18]. We also recorded whether patients received diuretics during their ICU stay, whether they had a mechanical ventilation (MV) requirement, number of days on MV, and duration of ICU- and hospital-stay. Patients were evaluated in terms of their 7th, 28th, and 60th day mortalities. Any mortality occurring after discharge from the ICU was detected by conducting a scan in the death notification system database.

Statistical analysis

Data analysis was carried out using IBM SPSS V23. The normality of the quantitative data was determined with the Shapiro Wilk test. Comparisons between normally distributed data across groups were evaluated with the independent samples *t*-test (a parametric test), and comparisons between non-normally distributed data were evaluated with the Mann Whitney *U* test. Comparisons of qualitative data were evaluated with the chi-square test. Changes in serum uric acid levels over time were analyzed with a repeated measures variance analysis. ROC analysis was used to determine cutoff values for uric acid levels. Associations between variables were analyzed with Spearman's correlation test. Values of $p < 0.05$ were considered significant.

RESULTS

Patient characteristics

Of the 128 patients included in this study, 60 (46.8%) were female and 68 (53.1%) were male. The mean age of all patients was 60.39 ± 19.81 years. Regarding ICU admission diagnoses, the most common reasons for ICU admission were intracranial pathologies (30 cases, 23.4%), respiratory reasons (27 cases, 21.1%), general body traumas (24 cases, 18.8%), and cardiac reasons (19 cases, 14.8%). The most common comorbid states were hypertension (50 cases, 39.1%), diabetes mellitus (27 cases, 21.2%), and arrhythmia (26 cases, 20.3%). The most common causes for ICU admission and comorbidities are presented in Figures 1 and 2.

Comparisons between the survival/non-survival patient groups

Among ICU admission diagnoses, intracranial pathologies were associated with significantly higher mortality rates (63.3%) than other admission diagnoses (35.7%) ($p = 0.014$). In addition, the mortality rates among patients admitted to the ICU due to trauma (20.8%) were significantly lower than the mortality rates of other diagnoses (47.1%) ($p = 0.034$).

When comparing the survival and non-survival groups, the C-reactive protein (CRP) level at time of ICU admission was significantly higher in the non-survival group (18.35 mg/L (0.3 - 329) compared to the survival group (8.59 mg/L (0.07 - 191)) ($p = 0.001$). In addition, both the SOFA and APACHE II scores at the time of ICU admission were significantly lower in the survival group (5 (0 - 15); 14 (2 - 31), respectively) compared to the non-survival group (7 (1 -15); 17.5 (6 - 38), respectively) ($p = 0.001$, $p = 0.001$, respectively). Further, the number of ICU days on mechanical ventilation was significantly lower in the survival group (1 (0 - 71)) compared to the non-survival group (9 (0 - 35)) ($p < 0.001$). Table 1 presents data from the survival and non-survival groups.

Comparison of serum uric acid and other variables

The median uric acid level of all of the included patients on the first day of ICU admission was 4.6 (1.2 - 36) mg/dL. ICU-admission uric acid levels were < 2.6 mg/dL in 22 patients (17.2%), > 7 mg/dL in 31 patients (24.2%), and between 2.6 - 7 mg/dL in 75 patients (58.6%). There was no significant difference in ICU-admission uric acid levels between the survival and non-survival groups ($p = 0.893$). The relationships between first day uric acid level and frequently observed or high-mortality conditions in the ICU were evaluated. At the time of admission, 6 patients had sepsis and 1 patient had ARDS. During ICU-stay, 7 patients (5.5%) developed ARDS and 7 (5.7%) developed sepsis. The median uric acid level was significantly higher in the patient subset with ARDS (9.2 (6.90 - 12) mg/dL) compared to those without ARDS (4.45 (1.2 - 36) mg/dL) ($p = 0.001$). The median uric acid level measured during the first three days of ICU stay was significantly higher in the patient subset with sepsis (9.2 (4.5 - 36) mg/dL) compared to those without sepsis (4.4 (1.2 - 22.9) mg/dL ($p = 0.02$). The AUC-ROC for ARDS for uric acid value was AUC: 0.854 (95% CI: 0.766 - 0.942). According to ROC analysis with regards to the probability of ARDS development, a uric acid cutoff level of 6.95 mg/dL yielded a sensitivity of 0.75 and a specificity of 0.79. The AUC-ROC for SEPSIS for uric acid value was AUC: 0.79 (95% CI: 0.669 – 0.911). According to ROC analysis with regards to the probability of sepsis development, a uric acid cutoff level of 5.5 mg/dL yielded a sensitivity of 0.66 and a specificity of 0.67. Figures 3 and 4 show ROC curves for ARDS and sepsis, respectively.

There was a significant but weak positive correlation between first day uric acid level and APACHE II score in the deceased patients ($r = 0.361$, $p = 0.007$). This correlation was not detected with the SOFA score (Figure 5). According to the Cox regression analysis, first day uric acid level was not determined to be a significant risk factor according to hospital stay length or hospital mortality days ($p = 0.904$ and $p = 0.787$, respectively). In addition to uric acid levels measured on specific days, the time-dependent change of uric acid levels was analyzed. When the time factor was included in the binary logistic regression model as an independent variable, it was found that time did not have a significant effect on mortality; however, uric acid was detected as a significant risk factor. Elevation of uric acid level was associated with a 1.093 times higher risk of mortality. In the survival and non-survival groups, there were no significant differences between first day median uric acid levels and the 7th, 28th, and 60th day mortalities ($p = 0.413$, $p = 0.201$, $p = 0.708$, respectively).

In addition, first day uric acid level did not significantly correlate with ICU stay length or hospital stay length ($p = 0.118$, $p = 0.536$, respectively).

When comparing the last measured uric acid levels during ICU-stay, the median last uric acid level was 5.8 (0.8 - 14.7) mg/dL in the non-survival group, which was

Table 1. Data from the survival and non-survival groups.

	Survival	Non-Survival	Total	p
BMI * (kg/m^2)	26.94 ± 3.81	26.03 ± 3.64	26.56 ± 3.75	0.175
Pulse rate * (/minute)	99.69 ± 24.32	101.46 ± 27.24	100.44 ± 25.5	0.704
Systolic BP * (mmHg)	120.28 ± 29.05	120.76 ± 26.97	120.48 ± 28.08	0.924
Diastolic BP * (mmHg)	69.57 ± 16.33	73.63 ± 17.55	71.28 ± 16.9	0.186
pH *	7.35 ± 0.12	7.35 ± 0.13	7.35 ± 0.12	0.899
Lactate * (mmol/L)	2.32 ± 2.13	3.88 ± 2.78	2.98 ± 2.54	**0.001**
Na * (mEq/L)	137.57 ± 7.51	138.49 ± 4.64	137.96 ± 6.45	0.397
K * (mEq/L)	3.98 ± 0.72	3.99 ± 0.72	3.99 ± 0.72	0.989
Mg ** (mg/dL)	1.16 (0.55 - 2.12)	0.93 (0.47 - 2.93)	0.98 (0.47 - 2.93)	0.102
BUN ** (mg/dL)	25 (0.87 - 239)	20.55 (9.1 - 173)	22.5 (0.87 - 239)	0.707
Creatinine ** (mg/dL)	0.89 (0.35 - 2.63)	1.0 (0.4 - 12)	0.94 (0.35 - 12)	0.377
Albumin * (g/dL)	3.13 ± 0.64	2.98 ± 0.84	3.07 ± 0.73	0.282
ALT ** (U/L)	18.75 (4 - 1208)	18 (3 - 608)	18 (3 - 1208)	0.912
AST ** (U/L)	24 (10 - 821)	26.10 (11 - 546)	25 (10 - 821)	0.263
Hgb * (g/dL)	11.8 ± 2.24	11.85 ± 2.4	11.82 ± 2.3	0.896
CRP ** (mg/dL)	8.59 (0.07 - 191)	18.35 (0.3 - 329)	12.75 (0.07 - 329)	**0.001**
SOFA score **	5 (0 - 15)	7 (1 -15)	6 (0 - 15)	**0.001**
APACHE score **	14 (2 - 31)	17.5 (6 - 38)	16 (2 - 38)	**0.005**
MV days **	1 (0 - 71)	9 (0 - 35)	5 (0 - 71)	**≤ 0.001**
ICU stay length **(day)	11 (2 - 83)	12 (2 - 58)	11 (2 - 83)	0.226
Uric acid level at admission ** (mg/dL)	4.65 (1.2 - 36)	4.3 (1.2 - 22.9)	4.6 (1.2 - 36)	0.893

*** - shown as mean ± std. deviation, ** - shown as median (min - max). Statistically significant differences between survival and non-survival groups are underlined.**
Abbreviations: BMI - body mass index, CRP - C-reactive protein, BP - blood pressure.

Table 2. Uric Acid trend - Time - Mortality Cox regression analysis.

	β	SH	p	Exp (β)
Time	-0.034	0.018	0.056	0.967
Uric Acid	0.089	0.027	0.001	1.093
Fixed	-0.505	0.172	0.003	

Table 3. Analysis of last uric acid level – mortality.

	Mortality		p
	Yes	No	
Uric Acid (mg/dL)	5.8 (0.8 - 14.7)	3.8 (0.9 - 8.7)	**0.001**
Proportion of last 2 values	1.17 (0.26 - 2.77)	0.95 (0.26 - 2.13)	**≤ 001**

Statistically significant differences between survival and non-survival groups are underlined.

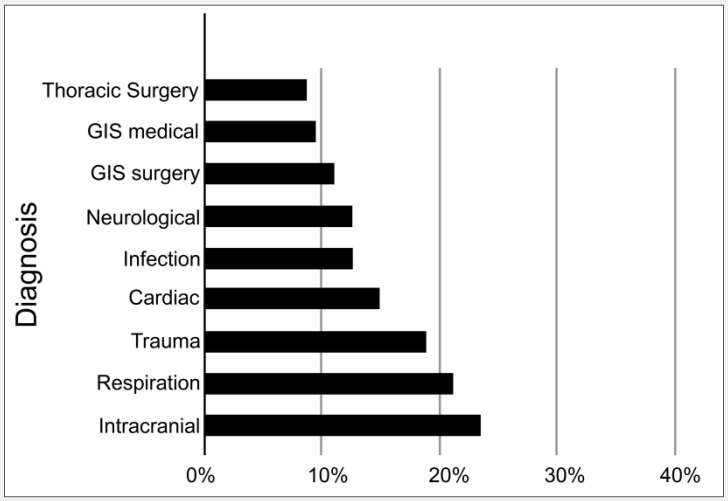


Figure 1. Diagnoses for ICU Admission.

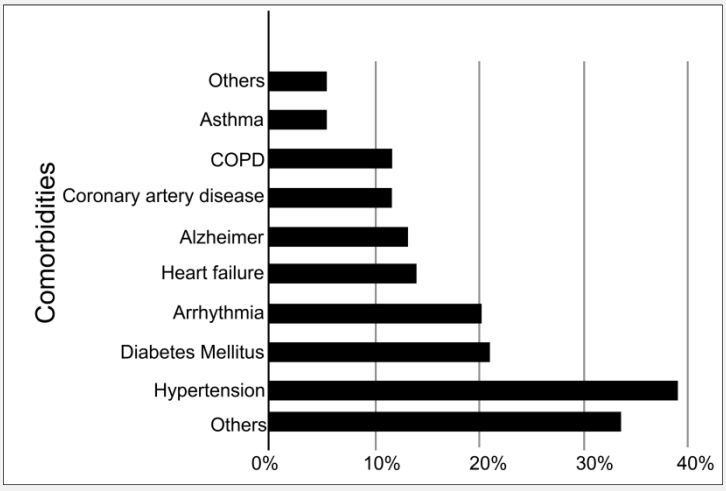


Figure 2. Comorbidities of the study group.

significantly higher than that of the survival group (3.8 (0.9 - 8.7) mg/dL) (p = 0.001). The AUC-ROC for mortality for last uric acid value was AUC: 0.674 (95% CI: 0.575 - 0.772). According to ROC analysis with regards to the probability of mortality development, a uric acid cutoff level of 4.5 mg/dL yielded a sensitivity of 0.63 and a specificity of 0.62. A last uric acid level measured before mortality in the ICU > 4.5 mg/dL was associated with a 2.638 times higher risk (relative risk) for mortality.

For those patients who stayed in ICU long enough to allow at least 2 uric acid measurements (115 patients), the last two uric acid levels (measured before discharge or mortality) were evaluated. Accordingly, while the medi-

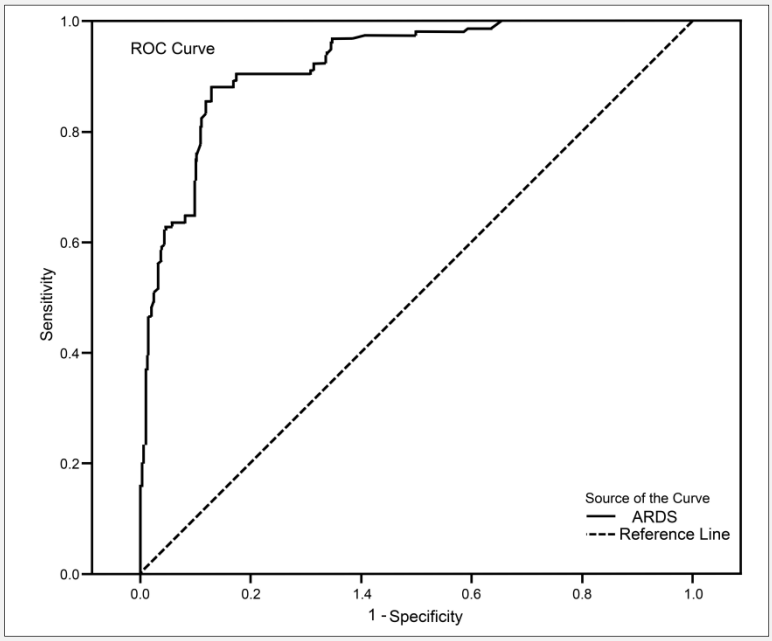


Figure 3. ARDS - Uric acid ROC curve (*ARDS-Uric Acid ROC curve, Abbreviations: ARDS; acute respiratory distress syndrome).

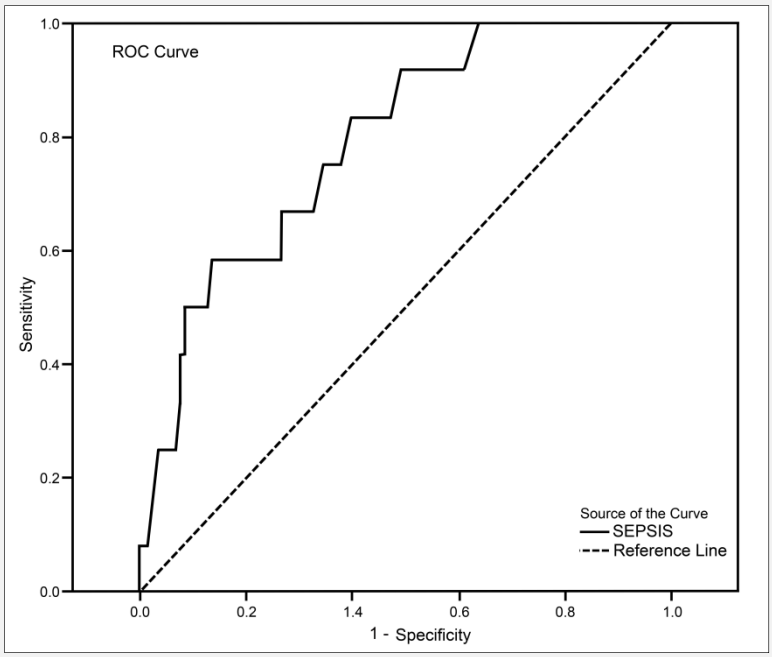


Figure 4. Sepsis - Uric acid ROC curve (* Sepsis-Uric Acid ROC curve).

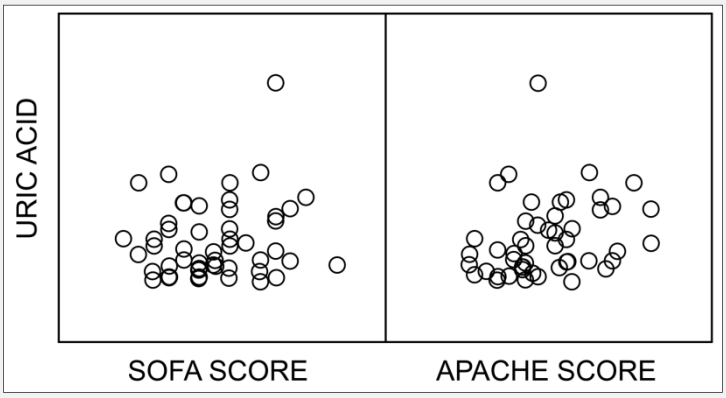


Figure 5. Scatter diagrams of uric acid level plotted against SOFA and APACHE II scores in the non-survival groups.

an uric acid level was increased 1.17 (0.26 - 2.77) times in the non-survival group, it was increased 0.95 (0.26 - 2.13) times in the survival group, which was significant ($p < 0.001$). The AUC-ROC for mortality for the last two uric acid ratio values was AUC: 0.714 (95% CI: 0.615 – 0.813). According to ROC analysis with regards to the probability of mortality development, a cut-off ratio of the last two uric acid levels of 1.5 yielded a sensitivity of 0.21 and a specificity of 0.96. A 1.5-fold increase in the uric acid level predicted mortality with a positive predictive value of 92.6% and a negative predictive value of 65.2%.

DISCUSSION

The present study primarily aimed to evaluate the association between blood uric acid level (and its trend) and mortality in critically ill patients admitted to the ICU. The current results indicate that a 1.5-fold increase in the last two uric acid levels predicted mortality for deceased patients. A last uric acid value measured before mortality in the ICU > 4.5 mg/dL was associated with a 2.638-fold higher risk (relative risk) of mortality. Additionally, every 1 mg/dL increment in uric acid during follow-up was associated with a 1.093-fold higher risk of mortality. Blood uric acid level can vary with many clinical conditions and influences. In the capillary endothelium, xanthine oxidase is activated in serious infectious states, during ischemia of many organs, and during hypoxemia; it acts on xanthine and hypoxanthine to convert them to uric acid [19-22]. Based on this mechanism, uric acid has been described as a marker that can indicate disturbed oxidative metabolism and tissue hypoxia [11]. Additionally, increased uric acid levels have been shown in the fluid covering the human respiratory tract. This fluid is a physiological response to increased oxidative stress and has been suggested to be an antioxidant mechanism. In light of this finding, a recent large-scale clinical study suggested that uric acid may play a protective role against oxidative effects in the lungs and may protect pulmonary functions. That study reported a positive correlation between serum uric acid level and FVC% and FEV1% in a middle-aged healthy Korean population [23].

Many studies have shown that elevated uric acid levels are a potential risk factor for mortality in disorders such as sepsis, ARDS, cardiovascular disorders, kidney diseases, obesity, and diabetes mellitus [15,24-27]. However, there are few studies with regards to uric acid levels in the field of intensive care. The study by Aminiahidashti et al. prospectively evaluated 120 critically ill patients, and reported that 1st day uric acid level in ICU was not an independent variable for predicting mortality [14]. In another prospective cohort study, Hooman et al. examined 220 patients in the pediatric intensive care unit (PICU), and similarly, they did not find an association between 1st day uric acid level and mortality; however, they did find that mechanical ventilation and inotropic support requirements were associated with poor prognosis [28]. Another retrospective study including data from 471 ICU patients found no association between baseline serum uric acid level and infection prognosis [29]. Similarly, in our current study, we did not find a significant difference between first day uric acid value and 7th, 28th, and 60th day mortalities. The aforementioned studies examined only spot baseline uric acid levels in the ICU, and therefore, it is difficult to make any assumptions, as uric acid level is influenced by metabolic, physiological, and environmental factors. In our current study, we analyzed changes in uric acid levels occurring throughout ICU stay, and we found that a

1.5-fold increase in uric acid value could predict mortality with a positive predictive value of 92.6%. This data indicates the significance of uric acid as a simple and convenient biomarker for predicting mortality in critically ill patients. In many other studies, the cutoff value for elevated uric acid levels was defined as 7 - 8 mg/dL, and classifications were made according to this cutoff value [14,24,28,30]. The majority of our current patients were post-trauma patients requiring ICU admission; we did not include any patients with comorbidities and chronic diseases that can possibly elevate baseline uric acid levels. Possibly because of this reason, the mean uric acid level at time of admission in our current study was low. Although the blood uric acid levels measured throughout the ICU stay of some patients did not increase above the defined cutoff levels (> 6.5 mg/dL (390 μmol/L) or 7 mg/dL (420 μmol/L) for males and > 6 mg/dL (360 μmol/L) for females), our results show that an increase of a certain proportion is associated with clinical outcomes [4]. In addition, we did not find a significant association between the uric acid level measured at ICU admission and ICU stay length. Elevated uric acid levels have been shown to be present in conditions frequently requiring ICU admission such as ARDS, cardiac diseases, and COPD [10,15,30]. Particularly in ARDS, patients are exposed to high levels of oxygen, generally via xenobiotics or through the use of therapeutic medication. In addition, a significant association has been shown between the incidence of ARDS and low serum antioxidant level in patients with widespread inflammation, such as sepsis. Increased uric acid concentrations have been shown in the BAL fluid of patients with ARDS [31-33]. Lee et al. retrospectively reviewed data from 237 ARDS patients spanning a 6-year period, and reported that low uric acid level (< 3 mg/dL) was a prognostic marker for low in-hospital mortality [15]. In our current study, the median 1st day uric acid level was 9.2 (6.9 - 12) mg/dL in patients with ARDS at the time of ICU admission and 4.45 (1.2 - 36) mg/dL in patients who did not develop ARDS ($p = 0.001$) (Figure 3). This result suggests that uric acid may play a role in the increased vascular permeability, apoptosis, and fibrotic process in patients with ARDS, and that uric acid may be used as a biomarker that can be monitored in high-risk patients. Many studies have shown an association between uric acid and pulmonary diseases, including pulmonary embolism, acute COPD exacerbations, and ARDS [33-36], indicating that elevated uric acid levels may be associated with pulmonary inflammation processes.

Results of the present study also indicate that there is an association between elevated uric acid levels and an increased incidence of sepsis. We found that the median first day uric acid level was significantly higher in patients with sepsis (9.2 (4.5 - 36) mg/dL) compared to those without sepsis (4.35 (1.2 - 22.9 mg/dL) ($p = 0.002$) (Figure 4). It is thought that the antioxidant response is increased during sepsis in order to balance the excess proinflammatory cytokines and oxidative stress, resulting in immune system dysfunction. Uric acid is believed to be an indicator of oxidative stress in the sepsis pathway [37]. Considering that high levels of oxygen radicals and low antioxidant levels in patients with sepsis can lead to multi-organ failure, measurement of uric acid may be useful as a marker for oxidative stress in patients with sepsis. Indeed, Akbar et al. showed that elevated uric acid levels are associated with poor prognosis in patients with sepsis [24].

Another interesting finding of our current study was that there was a significant correlation between first day uric acid levels in the ICU and APACHE II scores (which were assessed on the same day). Similarly, Akbar et al. also reported a significant positive correlation between first day uric acid levels and APACHE II scores in patients with sepsis [24]. Scoring systems used in the ICU were primarily developed to determine the risk of mortality, and they often include laboratory findings in addition to various clinical data. Our current results suggest that elevated first day uric acid level can be included in ICU scores, particularly for patients with sepsis or ARDS. Chuang et al. compared data from 73 patients with sepsis or septic shock with a control group and found a positive correlation between elevated plasma uric acid level and APACHE II score [38]. The results of that study suggest that uric acid levels in patients with sepsis can be an indicator of total antioxidant capacity and can provide early information regarding outcomes.

There are some limitations to our current study. First, this study required a prospective follow-up, and the reliability of the results would have been enhanced with an increased sample size. Second, although patients were selected according to our exclusion criteria, we did not collect information regarding patient lifestyles and socioeconomic levels, which are likely to influence their baseline uric acid levels. Third, although we questioned patients regarding their allopurinol use and other similar clinical information that can influence uric acid levels, we did not examine in detail any other medical therapies that patients were continuously receiving. Fourth, the reliability of the results should be supported by the inclusion of a greater number of patients from different subsets (i.e., ARDS, sepsis, etc.).

CONCLUSION

The time-dependent increase of uric acid levels can be used as an important biomarker for predicting mortality in critically ill patients and should possibly be included in the current mortality risk scores. Indeed, elevated uric acid levels measured on the first day of ICU admission showed a positive correlation with first day APACHE II scores. Elevation of this simple, inexpensive, and readily available biomarker may additionally provide guidance in the diagnostic stage and in predicting outcomes of patients with sepsis and ARDS.

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Ethics Approval and Consent to Participate:
We state that all authors have read and approved the submission of the manuscript, and the manuscript has not been published elsewhere in whole or part in any language.
We started our study with the approval of the local ethics committee (Ondokuz Mayıs University Hospital, Samsun, Turkey) (2017/178).

Availability of Data and Materials:
All datasets are stored by corresponding author. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions:
Mehtap Pehlivanlar Küçük designed study and writing of paper, Ahmet Oğuzhan Küçük design of study, responsible for analysis of data and collection of data, Çağatay Erman Öztürk collected data, patient consultation, Mehmet Can Er collected data, Fatma Ülger is senior consultant of study. All authors made substantial contributions to the conception and design of the study, or acquisition of data, or analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; final approval of the version to be submitted.

Declaration of Interest:
The author(s) declare(s) that there is no conflict of interest.

References:

1. Fox IH. Metabolic basis for disorders of purine nucleotide degradation. Metabolism 1981;30(6):616-34 (PMID: 6262603).
2. Oda M, Satta Y, Takenaka O, Takahata N. Loss of urate oxidase activity in hominoids and its evolutionary implications. Mol Biol Evol 2002;19(5):640-53 (PMID: 11961098).
3. Ayyildiz S. Analysis of Uric Acid Elevation. JAREM 2016;6:74-7 doi:10.5152/jarem.2016.1028. http://www.jarem.org/eng/ozet/409/32/Abstract
4. Johnson RJ, Kang DH, Feig D, et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension 2003;41(6):1183-90 (PMID: 12707287).
5. Anker SD, Leyva F, Poole-Wilson PA, Kox WJ, Stevenson JC, Coats AJ. Relation between serum uric acid and lower limb blood flow in patients with chronic heart failure. Heart 1997;78(1):39-43 (PMID: 9290400).
6. Vasquez-Vivar J, Santos AM, Junqueira VB, Augusto O. Peroxynitrite-mediated formation of free radicals in human plasma: EPR detection of ascorbyl, albumin-thiyl and uric acid-derived free radicals. Biochem J 1996;314(Pt 3):869-76 (PMID: 8615782).
7. Naghavi M, John R, Naguib S, et al. pH Heterogeneity of human and rabbit atherosclerotic plaques; a new insight into detection of vulnerable plaque. Atherosclerosis 2002;164(1):27-35 (PMID: 12 119190).
8. Batra S, Kumar R, Kapoor AK, Ray G. Alterations in antioxidant status during neonatal sepsis. Ann Trop Paediatr 2000;20(1):27-33 (PMID: 10824210).
9. Duran M, Kalay N, Akpek M, et al. High levels of serum uric acid predict severity of coronary artery disease in patients with acute coronary syndrome. Angiology 2012;63(6):448-52 (PMID: 22096206).
10. Bartziokas K, Papaioannou AI, Loukides S, et al. Serum uric acid as a predictor of mortality and future exacerbations of COPD. Eur Respir J 2014;43(1):43-53 (PMID: 23645404).
11. Elsayed NM, Nakashima JM, Postlethwait EM. Measurement of uric acid as a marker of oxygen tension in the lung. Arch Biochem Biophys 1993;302(1):228-32 (PMID: 8470901).
12. Ruggiero C, Cherubini A, Ble A, et al. Uric acid and inflammatory markers. Eur Heart J 2006;27(10):1174-81 (PMID: 16611671).
13. Riabov GA, Ladygin SS, Azizov IuM. [The concentration of end products of purine metabolism as possible signs of tissue hypoxia in critically ill surgical patients]. Anesteziol Reanimatol 1993(4): 41-3 (PMID: 8239027).
14. Aminiahidashti H, Bozorgi F, Mousavi SJ, Sedighi O, Gorji AM, Rashidian H. Serum Uric Acid Level in Relation to Severity of the Disease and Mortality of Critically Ill Patients. J Lab Physicians 2017;9(1):42-6 (PMID: 28042216).
15. Lee HW, Choi SM, Lee J, et al. Serum Uric Acid Level as a Prognostic Marker in Patients With Acute Respiratory Distress Syndrome. J Intensive Care Med 2017:885066617698911 (PMID: 28351229).
16. Pascual C, Karzai W, Meier-Hellmann A, et al. Total plasma antioxidant capacity is not always decreased in sepsis. Crit Care Med 1998;26(4):705-9 (PMID: 9559608).
17. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307 (23):2526-33 (PMID: 22797452).
18. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Crit Care Med 2017;43(3):304-77 (PMID: 28098591).
19. Ghiselli A, Serafini M, Natella F, Scaccini C. Total antioxidant capacity as a tool to assess redox status: critical view and experimental data. Free Radic Biol Med 2000;29(11):1106-14 (PMID: 11121717).

20. MacKinnon KL, Molnar Z, Lowe D, Watson ID, Shearer E. Measures of total free radical activity in critically ill patients. Clin Biochem 1999;32(4):263-8 (PMID: 10463818).

21. Meneshian A, Bulkley GB. The physiology of endothelial xanthine oxidase: from urate catabolism to reperfusion injury to inflammatory signal transduction. Microcirculation 2002;9(3):161-75 (PMID: 12080414).

22. Terada LS, Guidot DM, Leff JA, et al. Hypoxia injures endothelial cells by increasing endogenous xanthine oxidase activity. Proc Natl Acad Sci USA 1992;89(8):3362-6 (PMC 48867).

23. Song JU, Hwang J, Ahn JK. Serum uric acid is positively associated with pulmonary function in Korean health screening examinees. Mod Rheumatol 2017;27(6):1057-65 (PMID: 28693364).

24. Akbar SR, Long DM, Hussain K, et al. Hyperuricemia: An Early Marker for Severity of Illness in Sepsis. Int J Nephrol 2015;2015: 301021 (PMID: 26294973).

25. Billiet L, Doaty S, Katz JD, Velasquez MT. Review of hyperuricemia as new marker for metabolic syndrome. ISRN Rheumatol 2014;2014:852954 (PMID: 24693449).

26. Dawson J, Jeemon P, Hetherington L, et al. Serum uric acid level, longitudinal blood pressure, renal function, and long-term mortality in treated hypertensive patients. Hypertension 2013;6(1):105-11 (PMID: 23690348).

27. Zuo T, Liu X, Jiang L, Mao S, Yin X, Guo L. Hyperuricemia and coronary heart disease mortality: a meta-analysis of prospective cohort studies. BMC Cardiovasc Disord 2016;16(1):207 (PMID: 27793095).

28. Hooman N, Mehrazma M, Nakhaii S, et al. The value of serum uric Acid as a mortality prediction in critically ill children. Iran J Pediatr 2010;20(3):323-9 (PMID: 23056724).

29. Zhu HC, Cao RL. The relationship between serum levels of uric acid and prognosis of infection in critically ill patients. World J Emerg Med 2012;3(3):186-90 (PMID: 25215061).

30. Okazaki H, Shirakabe A, Kobayashi N, et al. The prognostic impact of uric acid in patients with severely decompensated acute heart failure. J Cardiol 2016;68(5):384-91 (PMID: 27261247).

31. Leff JA, Parsons PE, Day CE, et al. Serum antioxidants as predictors of adult respiratory distress syndrome in patients with sepsis. Lancet 1993;341(8848):777-80 (PMID: 8095998).

32. Newman JH, Loyd JE, English DK, Ogletree ML, Fulkerson WJ, Brigham KL. Effects of 100% oxygen on lung vascular function in awake sheep. J Appl Physiol Respir Environ Exerc Physiol 1983;54(5):1379-86 (PMID: 6345493).

33. Schmidt R, Luboeinski T, Markart P, et al. Alveolar antioxidant status in patients with acute respiratory distress syndrome. Eur Respir J 2004;24(6):994-9 (PMID: 15572544).

34. Lopez IH. Serum Uric Acid Levels Among Patients With Chronic Obstructive Pulmonary Disease. Chest 2003;124(4):168S. http://journal.chestnet.org/article/S0012-3692(16)60369-0/abstract

35. Shimizu Y, Nagaya N, Satoh T, et al. Serum uric acid level increases in proportion to the severity of pulmonary thromboembolism. Circ J 2002;66(6):571-5 (PMID: 12074276).

36. Wu VC, Huang JW, Hsueh PR, et al. Renal hypouricemia is an ominous sign in patients with severe acute respiratory syndrome. Am J Kidney Dis 2005;45(1):88-95 (PMID: 15696447).

37. Cowley HC, Bacon PJ, Goode HF, Webster NR, Jones JG, Menon DK. Plasma antioxidant potential in severe sepsis: a comparison of survivors and nonsurvivors. Crit Care Med 1996;24(7): 1179-83 (PMID: 8674332).

38. Chuang CC, Shiesh SC, Chi CH, et al. Serum total antioxidant capacity reflects severity of illness in patients with severe sepsis. Crit Care 2006;10(1):R36 (PMID: 16507162).