Hyperuricemia as a prognostic indicator in critically ill patients with sepsis: A prospective cohort study

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Abstract

Introduction: Uric acid activates proinflammatory markers and also has antioxidant property. Sepsis is a condition in which there is increased oxidative stress and lower antioxidant levels which results in dysfunction of multiple organs. In patients with sepsis uric acid could be utilized as an indicator of oxidative stress and worse prognosis.

Methods: Prospective data was collected for 18 months in the ICU of our hospital and theorized that in patients with sepsis elevated uric acid is a indicator of poor prognosis. The primary outcome was to examine the association between uric acid levels in patients presenting with sepsis and morbidities like Acute kidney injury (AKI), Acute respiratory distress syndrome (ARDS), duration of ICU stay and mortality. Supplementary end points were the need for renal replacement therapy and mechanical ventilation. Severity of illness was measured using the SOFA score.

Results: Overall 160 sepsis patients were enrolled. 68 (42.5%) patients had hyperuricemia. The overall morbidity rate

was 80.3%. The possibility of having a uric acid value of <7mg/dL along with AKI is 13.1% and without AKI is 86.9%, Meanwhile the possibility of havinga uric acid value of ≥7mg/dL along with AKI is 73.5% and without AKI is 26.5% (p value < 0.0001). Among patients with hyperuricemia and AKI, 42% required renal replacement therapy. Hyperuricemia was also associated with prolonged duration of ICU stay and higher SOFA scores.

Conclusions: In patients with sepsis elevated uric acid levels on admission to the ICU are associated with poor prognosis. Sepsis patients are at an enhanced risk for AKI, renal replacement therapy as well as prolonged duration of ICU stay.

Keywords: Hyperuricemia, Uric acid, Sepsis, Critical care, SOFA score, Acute kidney injury.

Introduction

Uric acid with the formula $C_5H_4N_4O_3$is a heterocyclic amalgam of carbon, hydrogen, nitrogen, and oxygen. Uric acid is the finishingresult of purine nucleotides metabolism. Nearly 75% of the uric acid is eliminated by the kidney and the remaining 25% is eliminated by the gastrointestinal tract. Glomeruli filtersalmost all the uric acid. Excretion of uric acid is controlled by post glomerular secretion as well as reabsorption. The proximal convoluted tubule is the site of uric acid secretion and reabsorption. About 90% of uric acidis reabsorbed into the blood by transporters that exchange intracellular anions. Urine excretes about 10% of the filtered uric acid [1].“Normal levels of blood uric acid are typically 3.4–7.2mg/dL for men and 2.4–6.1mg/dL for women” [2]. Hyperuricemia occurs due to increased production, decreased excretion, or both.

Experimental studies have shown that “the release of chemokine monocyte chemoattractant protein-1, 25 and interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumour necrosis factor-α (TNF-α) synthesis is stimulated by uric acid” [3].The expression of C- reactive protein in endothelial cells and smooth muscle cells is stimulated by uric acid. Uric acid may induce inflammation by two mechanisms- uric acid crystal precipitation causing inflammasome activation or assembly of free radicals in response to xanthine oxidase activity. Antioxidant capacity of uric acid is renowned which can be attributed to the presence of double bonds. Prooxidant molecules, such as hydrogen peroxide, hydroxyl radicals, and peroxynitrite can be

neutralized by uric acid. Hence uric acid has both oxidation and antioxidation properties [4].Several studies have shown correlation between uric acid and cardiovascular diseases, renal disease, and diabetes mellitus [5-7].

Sepsis is the body's reaction to an infection which could be potentially life-threatening. In sepsis, the free radical concentration is found to be increased as compared to the decrease in the antioxidant concentration. A disparity between oxidant and antioxidant status is assumed to be present in septic shock. Thus, in patients with sepsisuric acid levels could possibly be used as an indicator of oxidative stress. Studies in this regard are very few. Therefore, we studied patients with sepsis admitted in our Intensive care unit (ICU) from September 2017 to April 2019 to study whether uric acid can predict morbidities like Acute kidney injury (AKI), Acute respiratory distress syndrome (ARDS), duration of ICU stay and mortality.

Materials and Methods

We conducted a prospective cohort study among patients admitted to the ICU of our hospital from September 2017 to April 2019. Written informed consent was obtained from all the participants and the study was approved by the Ethics Committee.

Inclusion criteria

Patients who were of age >18 years and satisfied the Surviving sepsis campaign 2012 definition for sepsis were included in the study [8].

Exclusion criteria

Patients with (1) previous history of gout, (2) genetic defects causing hyperuricemia, (3) chronic kidney disease, (4) chronic liver disease, (5) malignancies on chemotherapy and (6) drugs causing hyperuricemia were excluded.

Once patients met the enrollment criteria, blood samples were drawn for complete blood counts, renal function tests, liver function tests, arterial blood gas, uric acid levels on the day of admission. The patient details were obtained from the case records. Patients were followed up for the need for renal replacement therapy, mechanical ventilation, duration of stay in ICU and outcome. During our study all the patients continued to obtain standard management for their illnesses by the ICU team. Sepsis was defined based on the Society of Critical Care Medicine, Surviving Sepsis Campaign 2012 definition [8].We defined

hyperuricemia as uric acid level ≥7mg/dL in both males and females for the purpose of our study [2]. We defined Acute kidney injury (AKI) as an absolute increase in serum creatinine of ≥0.3mg/dL over a period of 48 hours based on the Acute kidney injury network (AKIN) definition [9].We calculated thesequential organ failure assessment score (SOFA) to help assess the severity of disease in the ICU patients [10].We defined Acute respiratory distress syndrome (ARDS) as per the Berlin definition [11].

The primary outcome was to study the association between hyperuricemia in patients presenting with sepsis and morbidities like Acute kidney injury (AKI), Acute respiratory distress syndrome (ARDS), duration of stay in ICU and mortality. Additional end points were the need for renal replacement therapy and mechanical ventilation.

Collected data was analyzed using SPSS version 24. Chi square test, student t-test were used. Linear regression was used to assess the linear association of SOFA score with uric acid. The receiver operating characteristic (ROC) curve was constructed to look for association between uric acid and mortality. A p value < 0.05 was considered as statistically significant.

Results

A total of 160 patients were enrolled in the study. All patients included in our study were above 18 years of age. The mean age was 52.2±14.6 years. Men constituted 55% of the study population and 45% were women. Among 160 patients, 68 (42.5%) of them had hyperuricemia. In patients with hyperuricemia males were 42 (47.8%) and females were 26 (36.1%) (Table-1). The most prevalent comorbidities among patients with hyperuricemia were diabetes mellitus (43.8%), cerebrovascular accident (41.2%), hypertension (39.4%) and ischemic heart disease (36%).

Among hyperuricemia patients the overall morbidity rate was 80.3% of which AKI accounted for 73.5% and 82.3% had ARDS. The probability of having hyperuricemia along with AKI is about 73.5% and without AKI is about 26.5%. However, the probability of having a uric acid value <7mg/dL along with AKI is 13.1% and without AKI about 86.9%. These probabilities are statistically significant with a p value of <0.001(Figure1) (Table-2). Of those 50 patients who had hyperuricemia and AKI, 42% required renal replacement

therapy. However, in the overall study population 24 patients (15%) ended up having renal replacement therapy. Majority of the study population did not require renal replacement therapy.

Figure 1-The distribution of the ratio of the patients by the presence of AKI. The patients whose serum uric acid levels were equal or more than 7.0mg/dL were significantly more frequent in the AKI group (n = 50, 73.5%) than in the no-AKI group (n = 18, 26.5%).

The probability of having hyperuricemia along with ARDS is about 82.3% and without ARDS is about 17.7%. Of those with ARDS 64.2% required mechanical ventilation. Meanwhile the probability of having a uric acid value <7mg/dL along with ARDS is 65.2% and without ARDS about 34.8%. Of those with ARDS 48.3% required mechanical ventilation. These probabilities are not statistically significant with a *p* value of 0.616 indicating no correlation between uric acid levels and ARDS (Table-2).

Duration of stay in the ICU helps to identify the degree of severity of illness of the ICU patients. We found that patients with hyperuricemia had longer duration of ICU stay [median (IQR)=8(3.5-11.5) days] as compared to patients with normal uric acid levels [median (IQR = 6.5(3.5-9.5) days] with a *p* value of 0.015 which is statistically significant (Table 3). This shows that hyperuricemia patients had a longer duration of stay in ICU.

30.9% (21 out of 68) of the patients with hyperuricemia had mortality as outcome and 30.4% (28 out of 92) of the patients with normal uric levels had mortality as outcome with *p* value of 0.952 which is statistically not significant, indicating no correlation between uric acid levels and mortality (Table 3). The receiver operating characteristic (ROC) curve was constructed to look for association between uric acid and mortality (Figure 2). The Area under the curve is 0.545 which indicates a fair association between uric acid and mortality. Uric acid level equal to or greater than 5.55 has 67.3% sensitivity and 54.1% specificity for predicting mortality as outcome.

Severity of illness

The SOFA score helps predict the severity of disease and the prognosis of the patients in the intensive care unit. For the purpose of our study, we categorized the initial SOFA score into two categories first a score up to 7 which predicts a mortality of 56% and

second a score from 8 to 15 which predicts a mortality of 70%. In our study in patients with hyperuricemia 47.1% had an SOFA score of 8 to 15 while 52.9% had an SOFA score of 7. The probability of having a uric acid level <7mg/dLwith an SOFA score of 8 to 15 was only 13.1% and with an SOFA score of 7 was 86.9%. This shows that the hyperuricemia group has a higher SOFA score with a median of 7 whereas in the group with uric acid level <7mg/dL has a lower SOFA score with a median of 3. These probabilities are statistically significant with a p value of <0.003. In addition, a linear correlation between the SOFA score and uric acid value was noted, p value of <0.001 (Figure 3).

Table 1- Baseline characteristics

Characteristics	Overall (%)	Uric acid ≥7mg/dL (%)	Uric acid <7mg/dL (%)	p value*
Age (M±SD)	52.2±14.6	50.2±15.1	53.6±14.2	0.5611
<30 years	15(9.4%)	5(33.4%)	10(66.6%)	
30–60 years	97(60.6%)	40(41.3%)	57(58.7%)	
>60 years	48(30.0%)	23(48.0%)	25(52.0%)	
Sex				0.1392
Males	88(55%)	42(47.8%)	46(52.2%)	
Females	72(45%)	26(36.1%)	46(63.9%)	
Comorbidities				
DM	64(40%)	28(43.8%)	36(56.2%)	0.5049
IHD	25(15.6%)	9(36%)	16(64%)	0.7721
HTN	61(38.1%)	24(39.4%)	37(60.6%)	0.8914
CVA	17(10.6%)	7(41.2%)	10(58.8%)	0.8489

*Chi square test

DM, diabetes mellitus; IHD, ischemic heart disease; HTN, hypertension; CVA, cerebrovascular accident

Table 2- AKI and ARDS

Characteristics	Uric acid ≥7mg/dL (%)	Uric acid <7mg/dL (%)	P value
AKI	50(73.5%)	12(13.1%)	<0.01*
no-AKI	18(26.5%)	80(86.9%)	
ARDS	56(82.3%)	60(65.2%)	0.616
no-ARDS	12(17.7%)	32(34.8%)	

AKI, acute kidney injury

Table 3 – Duration of stay and mortality in ICU.

Characteristics	Uric acid ≥7mg/dL (%)	Uric acid <7mg/dL (%)	P value
Duration of stay(days)	Median (IQR)	Median (IQR)	0.015*
	8(3.5-11.5)	6.5(3.5-9.5)	
Mean	Mean	Mean	0.952
Mortality	21(30.88%)	28(30.43%)	

* statistically significant

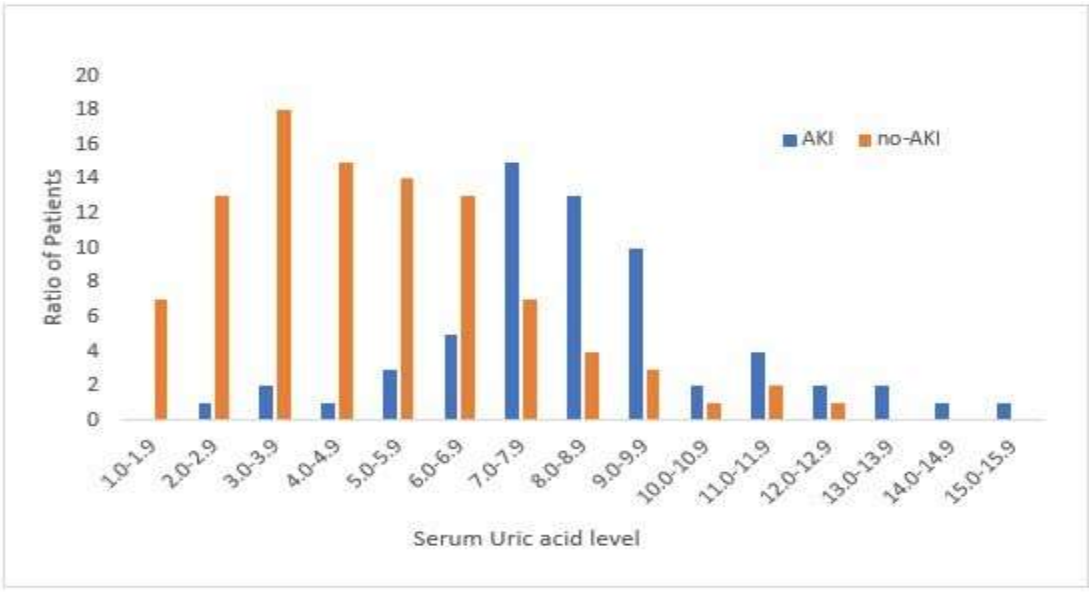

Figure 1-The distribution of the ratio of the patients by the presence of AKI. The patients whose serum uric acid levels were equal or more than 7.0mg/dL were significantly more frequent in the AKI group (n = 50, 73.5%) than in the no-AKI group (n = 18, 26.5%).

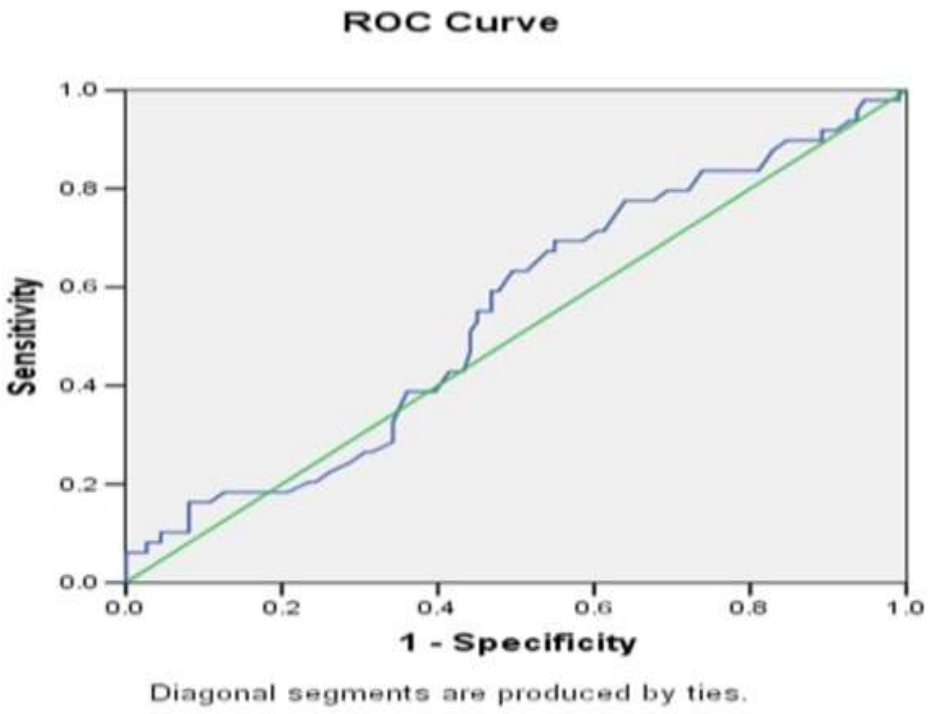

Figure 2-ROC curve for uric acid in predicting mortality.

ROC: Receiver operating characteristic

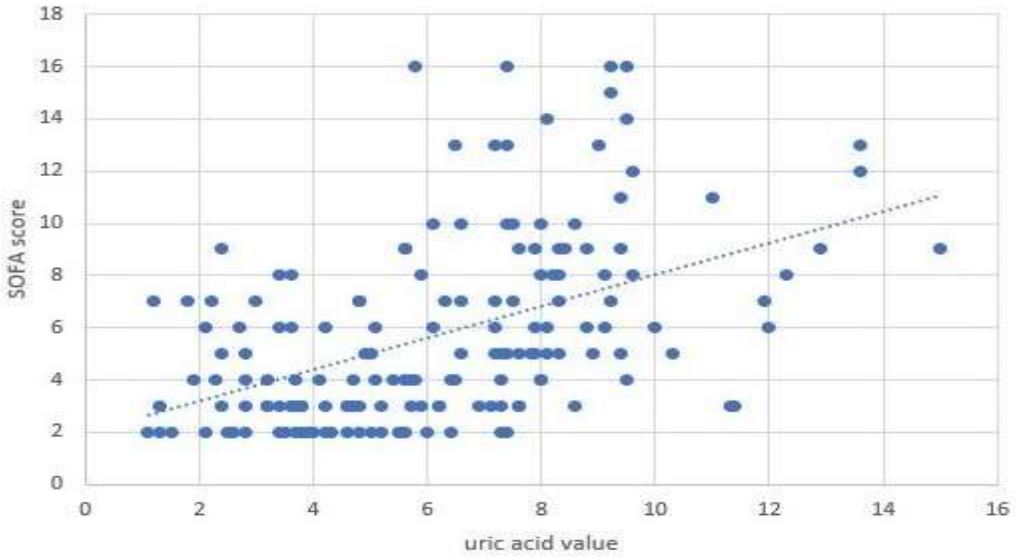

Figure 3- Scatter plot of Uric acid levels and SOFA score

SOFA: Sequential organ failure assessment score

Discussion

In our study, we found that raised uric acid levels on arrival to the ICU in patients with sepsis are associated with a poor prognosis. There is an increased risk for AKI, renal replacement therapy and increased duration of stay in the ICU. We hypothesize that during sepsis there is a disparity between oxidant and antioxidant status. There is an increased level of antioxidant response to counteract the excessive proinflammatory cytokines and this altered level of antioxidant defense leads to immune dysregulation and poorer outcomes. Uric acid activates NF-κ B which is a master switch for production of inflammatory markers and mediators. Oxygen-derived free radicals are released by endothelial cells and neutrophils when activated in a systemic inflammatory response. It appears that this oxygen derived free radicals play a significant role in causing or disseminating the systemic inflammatory response syndrome (SIRS). High uric acid levels in the sight of increased oxidative stress often have deleterious effects on various organs. Uric acid also has prominent antioxidant property to scavenge oxygen radicals and prevent deleterious effects on the tissues. Thus, uric acid acts as a double-edged sword overall the deleterious effects appear to outweigh the benefits of uric acid.

In our study the most significant finding is that hyperuricemia is associated with AKI in patients with sepsis. A study by Lapsia et al. [12] showed that preoperative serum uric acid of <7mg/dl was associated with increased incidence and risk for acute kidney injury, higher postoperative creatinine values, and longer hospital length of stay and duration of mechanical ventilation support in patients undergoing cardiac surgery. A similar study by Joung et al. [13] showed preoperative elevated uric acid (>6.5 mg/dL) was associated independently with AKI after cardiovascular surgery (odds ratio 1.46; 95% confidence interval 1.04–2.06, p =0.030). Sepsis patients are at risk for developing AKI due to changes in hemodynamics, exposure to medications like diuretics, changes in the functional capacity of other organs such as the heart and liver, and other comorbid factors. Uric acid itself can be a contributing factor. The mechanisms by which uric acid may contribute to AKI are renal vasoconstriction via inhibition of Nitric oxide synthase1, reduction in endothelial cell Nitric Oxide, and stimulation of the renin-angiotensin system. Other mechanisms include stimulation of inflammatory

cytokines like Monocyte chemoattractant protein-1, C-reactive protein, stimulation of oxidants and peroxynitrite-associated radicals and alteration of renal autoregulation [14].All these factors lead to direct or indirect injury to renal tubules ultimately leading to decreased glomerular filtration rate and renal dysfunction. Development of AKI during sepsis increases patient morbidity and mortality, has a significant effect on multiple organ functions, is associated with an increased length of stay in the intensive care unit, increases the need for renal replacement therapy and mechanical ventilation and hence consumes considerable healthcare resources. A recent study by Akbar et al [2] demonstrated the probability of having hyperuricemia along with AKI was 68.5% and without AKI was 31.5%. Meanwhile the probability of having a uric acid value <7mg/dL along with AKI was 18.9% and without AKI was 81.1% (p value < 0.0001). Hence uric acid may be an early indicator of impending AKI in patients with sepsis and could be used to predict the risk for AKI in septic patients.

Our study also found that there was a high incidence of ARDS noted in the study population, however there was no statistically significant association of hyperuricemia with ARDS. This is consistent with the results of an investigation conducted by Akbar et al[2] which found no association between uric acid levels and ARDS. In contrast to our finding, Aminiahidashti et al. [15] found that uric acid levels were higher among patients who needed mechanical ventilation. Also, Lapsia et al. [12] demonstrated that among patients undergoing non-transplant cardiovascular surgery, those with pre-operative plasma uric acid level more than 7mg/dl needed ventilator support for longer duration. Bartziokas et al. [16] demonstrated that patients with respiratory diseases having uric acid greater than 6.9 mg/dl had a need for prolonged ventilator support.

Our investigation also showed that patients with hyperuricemia had a longer duration of stay in the ICU. Similarly, Akbar et al. [2] found that hyperuricemia is associated greater chances of the patient being in ICU after 48 hours. Lapsia et al. [12] found that patients undergoing non-transplant cardiovascular surgery with pre-operative plasma uric acid levels more than 7 mg/dl had prolonged hospital stay. Similarly, Bartziokas et al. [16] conducted a research among patients with respiratory distress and found that hyperuricemia was

associated with a prolonged duration of stay in the ICU.

Elevated uric acid levels were not associated with increased mortality rate (p=.952) according to our study. ROC curve plotted to determine uric acid cut off to predict mortality showed a fair association between uric acid levels and mortality (AUC= 0.545). Aminiahidashti et al. [15] demonstrated that uric acid is not a predictor of mortality in critically ill patients. In contrast to our findings, Hooman et al. [17] found that children who had sepsis and high uric acid levels had an increased risk of mortality.

Our study also found that higher uric acid levels were associated with higher SOFA scores (p< 0.001) and patients with hyperuricemia had a longer duration of stay in the ICU. Similarly, Akbar et al. [2] found that hyperuricemia is associated greater chances of the patient being in ICU after 48 hours. Lapsia et al. [12] found that patients undergoing non-transplant cardiovascular surgery with pre-operative plasma uric acid levels more than 7 mg/dl had prolonged hospital stay.This suggests that hyperuricemia may be an early marker of poorer clinical outcomes in patients with sepsis. Thus, uric acid could be used as a marker like C-reactive protein (CRP) in predicting outcome in patients admitted with sepsis [18].

We recognize several limitations of this study, including modest sample size and short follow up period. There is a possibility that our patient population previously had an elevated uric acid level prior to developing sepsis which may be a factor increasing their risk of overall morbidity and mortality. Therefore, probably we should detect and potentially treat the general population for hyperuricemia to improve patient outcomes. The other limitations include that we have taken hyperuricemia as uric acid levels above 7 for both males and females. This could give a biased result since uric acid levels are higher in males by 1mg.

The other limitations include that we did not have the baseline creatinine on the patients from prior to admission and hence we did not know for certain what percentage of the patients had CKD prior to presentation. Thus, to minimize the degree of potential errors we used the patient's admission creatinine as the baseline value to mark the occurrence of AKI.

Other potential limitations include the fact that we did not serially measure uric acid levels during the course of the hospital

stay to see the trend of uric acid levels and outcomes. Our study paves the way for further randomized control trials with a larger sample size to confirm our findings.

Conclusions

Our study demonstrates that hyperuricemia is associated with an increased risk of AKI, need for renal replacement therapy, prolonged duration of stay in the ICU and higher SOFA scores. Elevated plasma uric acid levels are not associated with increased mortality in patients with sepsis. In conclusion hyperuricemia may be associated with poorer clinical outcomes in patients admitted to the ICU with sepsis.

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