E-ISSN: 2706-9575
P-ISSN: 2706-9567
IJARM 2023; 5(1): 77-79
Received: 08-10-2022
Accepted: 23-12-2022

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Analysis of uric hyperuricemia as early indicator of illness in sepsis condition

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DOI: https://doi.org/10.22271/27069567.2023.v5.i1b.450

Abstract
Background and Aim: Sepsis is a serious medical condition characterized by a whole-body inflammatory state and the presence of a known or suspected infection that has severe consequences. This study was conducted to bring out the correlation between hyperuricemia in clinically diagnosed sepsis patients and morbidity and mortality and also to find out the correlation between hyperuricemia in sepsis patients and acute kidney injury and ARDS in medical intensive care patients.
Material and Methods: The present study is the cohort study analysis; performed on the patients admitted to the medical intensive care unit in the medical college and associated hospital. We defined hyperuricemia as a uric acid level ≥7mg/dL in both males and females. We defined Acute Kidney Injury (AKI) as an absolute ≥0.3mg/dL increase in serum creatinine over a 48-hour time period from the baseline creatinine based on the Acute Kidney Injury Network (AKIN) definition. We used as the baseline creatinine value the patients' creatinine value at the time of initial presentation to the MICU.
Results: Among 150 study participants included in the study, 64 had elevated uric acid levels which constitutes about 43.8%, whereas 86 patients constituting 58.4% had normal uric acid levels. AKI was significantly higher in the hyperuricemia group. 77% of the septic patients with hyperuricemia developed AKI. The percentage of septic patients with normal uric acid levels developing AKI was 34.7%. Also, among the patients who developed AKI, 59.8% had hyperuricemia and 43.6% had normal uric acid levels. Similarly, 42.8% of patients with hyperuricemia developed ARDS whereas it was only 27.71% in the normal uric acid levels group.
Conclusion: Serum Uric acid may be potentially used as a marker of severity of illness as well as predictor of mortality and morbidity in patients with clinically diagnosed sepsis in the IMCU. This study recommends further studies on a large basis to confirm the observations.

Keywords: Acute kidney injury, hyperuricemia, serum uric acid, sepsis

Introduction
In humans uric acid is the final oxidative product of purine metabolism through the action of xanthine oxidase or xanthine dehydrogenase. Approximately two-thirds of uric acid is excreted by the kidney, and the rest is excreted by the gastrointestinal tract. In addition some uric acid is degraded in the body after reaction with oxidants or peroxynitrite [1, 2].
Since the last century elevated uric acid has noted to be associated with atherosclerosis hypertension, hyperinsulinemia and chronic kidney disease. Hyperuricemia is defined as accumulation of serum uric acid beyond its solubility point in water and develops due to uric acid overproduction, under-secretion, or both Uric acid can induce acute inflammation of the renal epithelial cells via uric acid crystals [3, 4].
Sepsis is a serious medical condition characterized by a whole-body inflammatory state and the presence of a known or suspected infection that has severe consequences. Hence majority of intensive care unit patients undergo ischemic-reperfusion injury and inflammation to varying degrees during their hospitalization [5-7].
Oxidative stress is found out by the presence of elevated serum uric acid which is a poor prognostic sign in case of patients with sepsis as multi organ dysfunction occurs as a result of high oxygen free radicals. Increased levels of serum uric acid causes acute activation of many transcription factors in patients with severe infection and is a poor prognostic sign in case of severe infection [2-8].
We were prompted to undertake this study as serum uric acid estimation is readily available and economical compared to newly evolving biomarkers in sepsis.

Hence this study was conducted to bring out the correlation between hyperuricemia in clinically diagnosed sepsis patients and morbidity and mortality and also to find out the correlation between hyperuricemia in sepsis patients and acute kidney injury and ARDS in medical intensive care patients.

Materials and Methods

The present study is the cohort study analysis; performed on the patients admitted to the medical intensive care unit in the medical college and associated hospital. The institutional ethical committee was informed about the study and the ethical clearance certificate was obtained prior to the start of the study. The patients were informed in detail about the study and written informed consent was obtained prior to the start of the study.

Inclusion criteria were age more than 18 years and admission to the MICU with a working diagnosis of sepsis based on the Society of Critical Care Medicine, Exclusion criteria were as follows: pregnant females, patients from an outside facility that have already been in the MICU for more than 24 hours, patient who denied consent, patient with history of kidney disease, patient with case of gout were excluded from the study.

Patient's data such as age, gender, comorbidities, ventilation status, need for renal replacement therapy, and duration of stay in the hospital was collected. We used the baseline creatinine value the patient's creatinine value at the time of initial presentation to medical intensive care unit. Once the patient met the inclusion criteria then blood samples were obtained for uric acid, basic metabolic profile, complete blood count, lactic acid, phosphorus, albumin, and arterial blood gas. Repeat samples for arterial blood gas and basic metabolic profile were obtained at 24 and 48 hours.

During the course of the study all patients continued to receive standard of care for their illnesses by the MICU team. For the purpose of our study we defined hyperuricemia as a uric acid level ≥7mg/dL in both males and females. We defined Acute Kidney Injury (AKI) as an absolute ≥0.3mg/dL increase in serum creatinine over a 48-hour time period from the baseline creatinine based on the Acute Kidney Injury Network (AKIN) definition. We used as the baseline creatinine value the patients' creatinine value at the time of initial presentation to the MICU.

We used as the baseline creatinine value the patients' creatinine value at the time of initial presentation to the MICU. Additional end points included need for renal replacement therapy and the patients' stability to be transferred to a lower level of care.

Statistical Analyses. Percentages of measures by uric acid level were compared using Chi squared tests for association. For APACHE II scores, linear regression was performed to assess the linear association with uric acid. All analyses were performed in SAS 9.4.

Results

In the study population, the median age was 56.48 years. 7.89% were under 30 years, 58% belonged to 30 - 65 years age group and contributed to the whole lot, followed by 39.55% in the ≥ 65years age group. Our study population had a slight male preponderance with 78 males found as compared to 72 females.

Among 150 study participants included in the study, 64 had elevated uric acid levels which constitutes about 43.8%, whereas 86 patients constituting 58.4% had normal uric acid levels. It can be inferred that among the study population, patients had type 2 diabetes mellitus as the most common comorbidity at 40%. The most prevalent co-morbidities among the patients with hyperuricemia were diabetes mellitus type 2 and type 1, decompensate liver disease and cerebrovascular accident. Patients without any comorbidities about 36% of the study population also developed sepsis.

The study participants were found to develop acute kidney injury, acute respiratory distress syndrome as the major complications. Our study aims at understanding the correlation between hyperuricemia and the secondary end points like AKI& ARDS. The aim of this study is to correlate between hyperuricemia and the complications like AKI & ARDS. AKI was significantly higher in the hyperuricemia group. 77% of the septic patients with hyperuricemia developed AKI. The percentage of septic patients with normal uric acid levels developing AKI was 34.7%. Also, among the patients who developed AKI, 59.8% had hyperuricemia and 43.6% had normal uric acid levels. Similarly, 42.8% of patients with hyperuricemia developed ARDS whereas it was only 27.71% in the normal uric acid levels group.

One of the end points of this study is the outcome of patient's status with regards to sepsis and its relation to hyperuricemia. In this study, it was found that out of the 64 patients with hyperuricemia, 56 had expired which constitutes 73.20% and 18 were discharged which is 26.8%. However, this was not statistically significant.

Table 1: Comparison of hyperuricemia and outcome of patients

Out com (n =150)	Uric acid > mg/dl	Uric acid < mg/dl	p-value
Death (N = 82)	56	46	0.12
Discharged (N = 68)	18	40	
Total	64	86	

Discussion

In this prospective cohort study, we report that elevated uric acid levels on arrival to the IMCU in patients with sepsis are associated with a poor prognosis; that is, an increased risk for AKI, ARDS, marks an increased duration of stay in the IMCU. Sepsis is a condition of increased pro inflammatory cytokines and oxidative stress thereby increases the antioxidants in the body to counterbalance. This altered level of antioxidant defense leads to immune dysfunction and poor outcomes. In a systemic inflammatory response, both endothelial cells and neutrophils are activated to release oxygen-derived free radicals [8, 9].

Systemic Inflammatory Response Syndrome (SIRS) in life threatening conditions is thought to be mainly due to the oxyradicals and that the imbalance in redox state reflects both oxidative stress and tissue damage. Serum uric acid, like other antioxidants such as albumin, bilirubin, or vitamins A, C, and E, is a powerful free radical scavenger. Uric acid increases in response to acute oxidative stress [8, 10]. Uric acid formation may even provide a significant antioxidant defense mechanism against nitration by peroxynitrite in rat heart during hypoxia. Hence uric acid is believed to be an important marker of oxidative stress. The mechanisms for increased uric acid are not well understood [2, 11].

Generally it is thought to due to both increased production as well as decreased excretion in sepsis. Severe sepsis and septic shock may induce free oxygen radical damage as well as ischemic changes, that further increases the change in xanthine/hypoxanthine to uric acid by activation of xanthine oxidase in microvascularendothelium. When there is accumulation and deposition of Uric acid in the blood vessels, the release of vasorelaxation factors is hampered,

vasoconstriction is interfered, leading to a series of pathophysiological processes and dysfunction of internal organs especially the kidney. Development of AKI during sepsis increases patient morbidity, predicts higher mortality, has a significant effect on multiple organ functions, is associated with an increased length of stay in the intensive care unit, and hence consumes considerable healthcare resources [12, 13].

The first important finding of our study is that hyperuricemia is associated with AKI in patients with early sepsis. When AKI develops, then it causes poor prognosis. For instance, the immediate operative and postoperative death rate after CVS surgery ranges between 1 to 2%, this rises to 10 to 38% if AKI develops and to >50% if dialysis is needed. Usually the patients with sepsis are a very complex subset of population who have MODS and bad prognosis and are usually very sick patients [14].

The important finding of our study was that hyperuricemia noted in the septic population correlated with an increased probability of having the patient still in the MICU at 72 hours. This again suggests that uric acid can be considered as an early and single marker and can help predict that those with an elevated uric acid level at initial presentation are more likely to be still in the IMCU at 72 hours versus those with a uric acid level less than 7mg/dL [15].

In our study we found that although there was a high incidence of ARDS noted in this septic patient population, there was no statistically significant association of hyperuricemia with ARDS. Thus although uric acid levels may be used to predict the severity of illness, duration of stay inIMCU, and risk for AKI, it was not significant enough to predict the incidence of ARDS.

This could potentially be due to the small patient population that we had for our study, especially since increasing uric acid levels have been reported by Nagaya *et al*. to correlate with clinical severity of primary pulmonary hypertension and has an independent association with long-term mortality of patient with primary pulmonary hypertension. This was most likely due to the small sample size [16].

Regarding the outcome of septic patients, though there was a slight increase in mortality among the hyperuricemic individuals with sepsis than those with normal Uric acid levels, it was statistically significant to prove the point.

One statistically significant end point was the correlation between mechanical ventilation and ARDS and AKI. It was statistically significant to see increased mechanical ventilation among patients with ARDS.

Conclusion

Serum Uric acid may be potentially used as a marker of severity of illness as well as predictor of mortality and morbidity in patients with clinically diagnosed sepsis in the IMCU. This study recommends further studies on a large basis to confirm the observations.

Conflict of Interest

Not available

Financial Support

Not available

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How to Cite This Article
Ughreja R. Analysis of uric hyperuricemia as early indicator of illness in sepsis condition. International Journal of Advanced Research in Medicine. 2023;5(1):77-79.