Hyperuricemia as an Early Marker in Predicting the Mortality and Morbidity in Patients with Sepsis

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ABSTRACT

Introduction: Serum uric acid can be used as a marker of oxidative stress, and poor prognosis in patients with sepsis, since high levels of oxy radicals, lower oxidant level in sepsis patients result in multi organ failure. Raised uric acid is associated with chronic diseases and is used as a prognostic indicator of severe infection as it acutely activates various transcription factors. Aim: This study aims to understand the correlation between hyperuricemia and the mortality and morbidity rate in patients with clinically suspected sepsis (based on Qsofa Criteria - Quick sepsis related organ failure). The secondary end points of the study are to understand correlation between hyperuricemia in clinically suspected sepsis patients and Acute kidney injury, acute respiratory distress syndrome, and duration of stay in the hospital.

Material and methods: We conducted a prospective cohort study in clinically suspected sepsis patients {based on the Qsofa Criteria} between September2017-2018 in a tertiary care center in AJ Institute Of Medical Sciences in South India. Patients or their medical power of attorneys provided written informed consent. A total no of 60 patients were enrolled based on the inclusion criteria, clinically suspected sepsis patients aged more than 18 years. All pregnant female, patients from outside facility admitted in the medical intensive care unit for more than 24 hours were excluded. For the purpose of our study we defined hyperuricemia as greater than or equal to 7 mg/ dl in both males and females. Patients were divided in two groups based on the uric acid levels. The first group had clinically suspected sepsis patients with uric acid levels more than 7 and the second group had clinically suspected sepsis patients with uric acid level less than 7.

Results: More than half of the patients, 55%, with high uric acid were found to be males. The overall mortality rate in patients with high uric acid levels was found to be 90%. The probability of having hyperuricemia with acute kidney injury was around 92.9%.

Conclusion: Hyperuricemia was associated with poor prognosis in clinically suspected sepsis patients.

Keywords: Hyperuricemia as an Early Marker in Predicting the Mortality and Morbidity in Patients with Sepsis

INTRODUCTION

Uric acid is end product of purine metabolism {through the action of xanthine dehydrogenase, xanthine oxidase} in humans. Purines are nitrogen containing compounds, endogenous or exogenous. Uric acid passes through the liver, enters the blood stream, most of it excreted in urine. Some uric acid is degraded in the body after reaction with oxidants or peroxynitrite.[1] Since the last century elevated uric acid has noted to be associated with atherosclerosis[2-6] hypertension, hyperinsulinemia[7,8] and chronic kidney disease.[9] 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[10]

Uric acid can induce acute inflammation of the renal epithelial cells via uric acid crystals. Uric acid may cause endothelial dysfunction and cause an afferent renal arteriolopathy and tubulointerstitial fibrosis in the kidney by activating the renin angiotensin aldosterone –system[11], activate various inflammatory transcription factors[12], and induce systemic cytokine production such as tumor necrosis factor alpha[13] and local expression of chemokines such as chemotactic protein 1 in the kidney and cox2 in the blood vessels.[14] This study was conducted in all patients coming to a tertiary care center in South India, who were admitted in Medical intensive care unit with a clinical diagnosis of sepsis based on QSOFA criteria. Hyperuricemia was defined more than 7 mg/dl in males and females. Acute kidney injury was defined an absolute >0.3 mg/dl increase in creatinine above the baseline in both males and females. q SOFA score (also known as quick SOFA) is a score that may identify patients with suspected infection who are at greater risk for a poor outcome. It uses three criteria, assigning one point for low blood pressure (SBP≤100 mmHg), high respiratory rate (≥22 breaths per min), or altered mentation (Glasgow coma scale<15). 2 or 3 points indicate high risk of poor outcome in patients with clinically suspected sepsis

Study aimed to find out the correlation between hyperuricemia in clinically suspected sepsis patient and morbidity and mortality rate and also to find out correlation between hyperuricemia in sepsis patients and acute kidney injury, ARDS, duration of stay in medical intensive care unit

MATERIAL AND METHODS

We conducted a prospective cohort study in clinically suspected sepsis patients with age more than 18 years, in medical intensive care unit in AJ institute of medical science

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a tertiary care hospital in South India from September 2017-2018. Informed consent was taken for the study. A total no of 60 patients with clinical diagnosis of sepsis based on the QSOFA criteria during the study period fulfilling the following inclusion criteria

Inclusion criteria

- All Patients admitted to medical intensive care unit with a clinical diagnosis of sepsis, age more than 18 years based on the QSOFA criteria.

Exclusion criteria

All pregnant females.

Patients from an outside facility, in medical intensive care unit for more than 24 hours.

Hyperuricemia was defined more than 7 mg/dl in males and females. Acute kidney injury was defined an absolute >0.3 mg/dl increase in creatinine above the baseline in both males and females. q SOFA score (also known as quick SOFA) is a score that may identify patients with suspected infection who are at greater risk for a poor outcome. It uses three criteria, assigning one point for low blood pressure (SBP≤100 mmHg), high respiratory rate (≥22 breaths per min), or altered mentation (Glasgow coma scale<15). 2 or 3 points indicate high risk of poor outcome in patients with clinically suspected sepsis. Once the patient met the inclusion criteria blood samples were obtained for uric acid, urea, creatinine, complete blood count, arterial blood gas analysis, serum electrolytes and chest x ray was done. Patients data such as age, gender, comorbidities, ventilation status, need for renal replacement therapy, 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. The primary end point was correlation between hyperuricemia in clinically suspected sepsis patients and morbidity and mortality rate. The secondary end points was correlation between hyperuricemia in clinically suspected sepsis patients and acute kidney injury, ARDS, duration of stay in hospital.

Sample size	n= 60	n=31	n=29
Uric acid		<7	>7
Mean Age	54.45+/-14.31	55.26+/-13.8	53.59+/-15
Age <30YR	2	0	2 {100%}
Age 31-64	42	23 {54.8%}	19{45.2%}
Age >65YR	16	8 {50%}	8 {50%}

Table-1: Age wise distribution

Sex	n=60	<7	>7	P
Male	40	18{45%}	22{55%}	0.14
Female	20	13{65%}	7{35%}	

Table-2: Gender wise distribution

STATISTICAL ANALYSIS

All statistical analysis was performed by SPSS software version 24. Descriptive statistics like mean and percentages were used for the analysis.

RESULTS

Age wise, genderwise distribution

All patients included in the study were above 18 years of age. Among the 60 patients, 40 were males 20 were females, in a mean age of 54.45+/-14.31. 29 patients out of the total 60 enrolled patients had hyperuricemia. In patients with hyperuricemia male were 22{55%} and females 7 {35%} (table-1).

Correlation between comorbidities and hyperuricaemia in clinically suspected patients

The probability of having acute kidney injury is about 92.9%

Comorbidities	n=60	>7	<7	P value
IHD	4	3{75%}	1{25%}	0.269
DM	14	9{64.3%}	5{35.7%}	0.173
HTN	17	11 {64.7%}	6{35.3%}	0.111
Acute kidney injury	28	26 {92.9%}	2{7.1%}	<0.001
Clinical features		<7	>7	
Altered sensorium	28	15 {53.6%}	13 {46.5%}	0.782
RR>22	48	24 {50%}	24 {50%}	0.605
Systolic<100	44	23 {52.3%}	21 {47.7%}	0.876
ARDS	8	1 {12.5%}	7 {87.5%}	0.017
Uric acid levels	6.87 +/-6.46	4.55 +/- 1.15	9.63 +/- 2.44	<0.001

Table-3: Distribution of comorbidities and clinical features in hyperuricaemia, and acute kidney injury

	n=60	<7	>7	P value
Duration	6.87+/-6.4	2.161.44	11.95.9	<0.001
Mortality	10	1{10%}	9{90%}	0.004

Table-4: Mortality and duration of stay in hospital

in patients with high uric acid levels. The probability of having uric acid level < 7 mg/dl along with acute kidney injury is 7.1%. The most prevalent comorbidities in patients with hyperuricemia is IHD {75%}, DM {64.3%}, and Hypertension {64.7%} (table-2).

Patients were selected based on the QSOFA criteria. 46.5% of the patients with hyperuricemia presented with altered sensorium. 87.5% of the patients with hyperuricemia had ARDS (table-3). Patients with clinically suspected sepsis with hyperuricemia shows 90% mortality and increased duration of stay in the hospital {<0.001} (table-4).

DISCUSSION

In the present prospective cohort study, hyperuricemia on admission to MICU in clinically suspected sepsis are associated with increased mortality and morbidity, that is increased risk of acute kidney injury, ARDS, increased duration of stay in the hospital.

During sepsis it is postulated that, increased level of antioxidant counterbalance the oxidative stress and pro inflammatory cytokines. This causes immune dysfunction and worst outcomes. In systemic inflammatory syndrome, both endothelial cells and neutrophils get activated to release oxygen free radicals.[15] The mechanisms for increased uric acid in sepsis is not known. It may be due to increased production and reduced excretion. Severe sepsis and septic shock may induce hypoxia or ischemia in multiple organs, which further increases the change in xanthine, hypoxanthine to uric acid through activation of xanthine oxidase in the microvascular endothelium in response to acute oxidative stress serum uric acid increases and it is a powerful free radical scavenger.[16,17] uric acid can cause kidney injury by direct tubular toxicity. It can also cause acute kidney injury secondary to the release of vasoactive mediators and oxidative stress. Many studies reported that levels the serum levels of uric acid could reflect the severity and prognosis of infection.[18-21] Rats with hyperuricemia have a significant increase in macrophage infiltration in their kidneys independent of crystal deposition[22] the development of acute kidney injury during sepsis increases the patient's morbidity mortality as it has a significant effect on multiple organ function and is associated with increased duration of stay in the hospital.

The present study had drawbacks-The patients included in the study had various underlying disorders and it was difficult to perform risk stratification during analysis. The modest sample size, enrollment of the patients from the MICU and not the surgical intensive care unit, and short follow up period. The other limitations included that we did not have a baseline creatinine on the patients from prior admission and hence did not know for certain what percentage of patients had CKD prior to the presentation.

CONCLUSION

Serum uric acids may be potentially used as a marker of severity of illness as well as predictor of mortality and morbidity in patients with clinically suspected sepsis. Further studies are required to confirm our observations and find the underlying mechanisms for hyperuricemia in sepsis.

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