E-ISSN: 2706-9575
P-ISSN: 2706-9567
IJARM 2021; 3(2): 30-33
Received: 17-05-2021
Accepted: 22-06-2021

Dr. Mamatha Pulloori
Assistant Professor, Department of General Medicine, MNR Medical College and Hospital, Sangareddy, Telangana, India

Dr. Kavangal Dhananjay
Assistant Professor, Department of General Medicine, Bhaskara Medical College, Moinabad, Rangareddy, Telangana, India

Corresponding Author:
Dr. Kavangal Dhananjay
Assistant Professor, Department of General Medicine, Bhaskara Medical College, Moinabad, Rangareddy, Telangana, India

Significance of hyperuricemia on the early diagnosis of disease severity in sepsis

Dr. Mamatha Pulloori and Dr. Kavangal Dhananjay

DOI: https://doi.org/10.22271/27069567.2021.v3.i2a.213

Abstract
Serum uric acid levels are an ideal marker in sepsis cases to assess oxidative stress and to predict disease prognosis. Elevated serum uric acid levels are associated with chronic disease conditions such as chronic kidney disease (CKD), cardiovascular disease (CVD). The present study was designed to assess the correlation between Hyperuricemia and mortality and morbidity in cases with clinically diagnosed sepsis. A total of 94 cases with a working diagnosis of sepsis above 18 years of age were recruited. The duration of hospital stay, mechanical ventilation, acute respiratory syndrome and acute kidney injury was noted. Patient discharge or death was considered an outcome of the sepsis. The most prevalent comorbidity was type 2 diabetes (44.68%), followed by type 1 diabetes (8.5%), type 2 diabetes with systemic hypertension (4.25%), chronic kidney disease (3.19%), cerebrovascular accident (3.19%), severe pulmonary disease (2.12%) and malignancy (2.12%). 59% cases had uric acid levels <7mg/dl and 41% had uric acid levels >7mg/dl. The comparison of uric acid levels with comorbidities (p=0.022), duration of hospital stay (p=0.003) and associated complications (p=0.003) was statistically significant. Hyperuricemia on patient arrival to the MICU with sepsis was associated with poor clinical outcome. High mortality rate was associated in cases with elevated uric acid levels.

Keywords: hyperuricemia, sepsis, mortality and morbidity, acute kidney injury (AKI), acute respiratory distress syndrome (ARDS)

Introduction
Hyperuricemia is termed as serum uric acid concentration higher than 7mg/dL or accumulation of serum uric acid beyond its solubility point in water due to excess or less secretion or sometimes both [1]. The prevalence of Hyperuricemia is approximately 8.9% to 24.4% in the general population [2, 3]. Normal levels of blood uric acid are typically 3.4-7.2mg/dL for men and 2.4-6.1mg/dL for women. Hyperuricemia directly or indirectly associated with various conditions like urolithiasis, gout, hypertension, chronic kidney disease (CKD), Hyperinsulinemia, atherosclerosis [4, 5]. Sepsis is a condition characterized by an inflammatory state of the body with severe known or unknown infection. Through its crystals, uric acid can influence the acute inflammation of renal epithelial cells and also have an impact on the body with its non-crystal effects. By activating the renin-angiotensin aldosterone system, uric acid may give rise to endothelial dysfunction and renal arteriolopathy and tubulointerstitial fibrosis in the kidney [6].
In critically ill cases in ICU, Hyperuricemia is an early marker of the severity of sepsis, as well as a predictor of acute kidney injury, acute respiratory distress syndrome, need for mechanical ventilation use and mortality [7]. Hence, the present study was designed to assess the correlation between Hyperuricemia and mortality and morbidity in cases with clinically diagnosed sepsis.

Material and Methods
The present prospective study was conducted in the Department of General Medicine at MNR Medical College and Hospital, Sangareddy from August 2019 to March 2021. A total of 94 cases with working diagnosis of sepsis were recruited. Cases above 18 years of age and cases admitted to MICU with working diagnosis of sepsis and cases willing to participate in the study were included. Pregnant and lactating women, known case of gout, cases from outside facility who have already been in the MICU for more than 24 hours and not willing to participate in the study were excluded.

Informed consent was obtained from all the study participants and study protocol was approved by institutional ethics committee.

All the patients who have admitted in the MICU were screened for sepsis. Blood samples were collected to screen CBC, urea, uric acid, creatinine and serum electrolytes. For the study reference, Hyperuricemia was defined as a uric acid level ≥7mg/dL in both males and females. Acute kidney injury (AKI) was defined as an absolute ≥0.3mg/dL increase in serum creatinine over a 48-hour time period from the baseline creatinine. The patients' creatinine value at the time of initial presentation to the MICU was considered as reference value. The duration of hospital stay, mechanical ventilation, acute respiratory syndrome and acute kidney injury was noted. Patient discharge or death was considered as outcome of the sepsis.

The SPSS version 23 was used to carry out statistical analysis relevant to the study. The frequency and percentages (%) were calculated. The chi-square test was used to test the significance of qualitative data. P-value of <0.05 was considered as statistically significant.

Results

Table 1: Demographic details of study participants (n=94)

Parameter	Frequency	Percentage
Age (In years)		
18-30	06	6.38%
31-50	32	34.04%
51-65	34	36.17%
>65	22	23.40%
Gender		
Male	49	52.12%
Female	45	47.87%
BMI		
<25	22	23.4%
25-30	32	34.04%
>30	40	42.55%
Comorbidities		
Without comorbidities	30	31.9%
Type-1 diabetes	08	8.5%
Type-2 diabetes	42	44.68%
Type-2 diabetes + systemic hypertension	04	4.25%
Chronic kidney disease	03	3.19%
Cerebrovascular accident	03	3.19%
Severe pulmonary disease	02	2.12%
Malignancy	02	2.12%
Duration of hospital stay		
>72 hours	43	45.74%
<72 hours	51	54.25%
Complications		
No complications	28	29.7%
ARDS	19	20.2%
Acute kidney injury (AKI)	41	43.61%
ARDS + AKI	06	6.38%

The hospital stay was more than 72 hours in 45.74% cases and <72 hours in 54.25% cases. The final outcome of the sepsis cases was lead towards discharge in 40.42% cases and death in 62.76% cases.

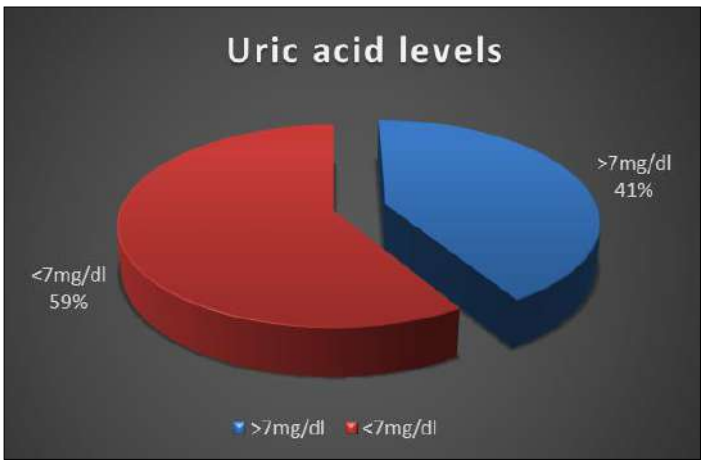

Fig 1: Uric acid levels in the study participants

Table 2: Comparison of uric acid levels (Hyperuricemia) with demographic variable in the study participants (n=94)

Parameter	Uric acid >7mg/dl (n=39)		Uric acid <7mg/dl (n=55)		p-value
	Frequency	Percentage	Frequency	Percentage	
Age (In years)					
18-30	3	7.69%	3	5.45%	0.564
31-50	15	38.46%	17	30.90%	
51-65	13	33.33%	21	38.18%	
>65	08	20.51%	14	25.45%	
Gender					
Male	22	56.41%	27	49.09%	0.218
Female	17	43.58%	28	50.90%	
Comorbidities					
Without comorbidities	14	35.89%	16	29.09%	0.022
Type-1 diabetes	07	17.94%	01	1.8%	
Type-2 diabetes	12	30.76%	30	54.54%	
Type-2 diabetes + systemic hypertension	02	5.12%	02	3.63%	
Chronic kidney disease	01	2.56%	02	3.63%	
Cerebrovascular accident	01	2.56%	02	3.63%	
Severe pulmonary disease	00	-	02	3.63%	
Malignancy	02	5.12%	00	-	
Duration of hospital stay					
>72 hours	24	61.53%	19	34.54%	0.003
<72 hours	15	38.46%	36	65.45%	
Associated Complications					
No complications	05	12.82%	23	41.81%	0.003
ARDS	8	20.51%	11	20%	
Acute kidney injury (AKI)	22	56.41%	19	34.54%	
ARDS + AKI	04	10.25%	02	3.63%	
Outcome of sepsis					
Discharged	14	35.89%	21	38.18%	0.538
Death	25	64.10%	34	61.81%	

Discussion

A total of 94 cases with a working diagnosis of sepsis above 18 years of age were recruited. Among the participants, majority of cases were between 51-65 years (36.17%), followed by 31-50 years (34.04%), above 65 years (23.40%) and 18- 30 years (6.38%). Male participants (52.12%) were more than female participants (47.87%) (Table 1). A study by Akbar SR *et al*. included 53.5% cases between 30-65 years, 39.6% cases above 65 years and 6.9% cases below 30 years with more male participants (57.6%) than female participants (42.4%) [1]. The BMI value in 23.4% cases was <25, 34.04% cases was 25-30 and in 42.55% cases was >30. (Table 1). A study by Akbar SR *et al*. noticed BMI between 18.5-24.9 was in 27.2% cases, BMI between 25-29.9 was in 25.09% cases and BMI above 30 in 47.8% cases [8].

In this study, 31.9% of cases had no comorbidities. The most prevalent comorbidity was type 2 diabetes in 44.68% cases, 8.5% had type 1 diabetes, 4.25% had type 2 diabetes with systemic hypertension, 3.19% had chronic kidney disease, 3.19% had cerebrovascular accident, 2.12% had a severe pulmonary disease and 2.12% had malignancy (Table 1). A study by Akbar SR *et al*. noticed diabetes mellitus was major comorbidity in 36.8% cases, followed by CAD in 25.7% cases, CVA in 16.7% cases, severe pulmonary disease in 16% cases, malignancy in 16% cases and CHF in 9.7% cases [8]. A study by Bagshaw SM *et al*. stated that septic patients have a greater burden of comorbid diseases (p<0.001) [12].

The major complication in the study participants was acute kidney disease (43.61%), followed by ARDS in 20.2% and ARDS with acute kidney disease in 6.38% cases. In 29.7% cases no complications were observed during the entire study (Table 1).

The duration of hospital stay was more than 72 hours in 54.25% of cases and less than 72 hours in 45.74% of cases. In this study, 59% of cases had uric acid levels <7mg/dl and 41% of cases had uric acid levels >7mg/dl (Figure 1). A study by Akbar SR *et al*. found that Duration of stay in the MICU helps indirectly identify the degree of severity of illness of the ICU patients. We found that overall 75% and54.2% of our enrolled patients were still in the MICU and not transferred to a lower level of care at 48 and 72 hours, respectively. The probability of having Hyperuricemia and still being in the MICU at 48 and 72 hours was 81.5% and 64.8%, respectively, while the probability of having a uric acid level <7mg/dL and being in the MICU at 48 and 72 hours was 71.1% and 47.8%, respectively [8]. In this study, Hyperuricemia was correlated with an increased probability of having a patient in the MICU for more than 72 hours. This indicates that a person with uric acid levels >7mg/dL likely to stay in MICU for more than 72 hours than the cases had uric acid levels <7mg/dL. The outcome of the sepsis cases was lead towards discharge in 40.42% of cases and death in 62.76% of cases. A study by Bagshaw SM *et al*. noticed that septic AKI was associated with a significantly higher rate of mortality than non-septic AKI, ICU and in hospital [12].

The comparison of uric acid levels with different age groups (p=0.564), gender (p=0.218) and final outcome of sepsis (0.538) was statistically not significant. The comparison of uric acid levels with comorbidities (p=0.022), duration of hospital stay (p=0.003) and associated complications (p=0.003) was statistically significant (Table 2). A study by Xialian Xu *et al*. stated that the relationship between Hyperuricemia and hospital mortality was not significant [10].

A study by Akbar SR *et al*. stated that elevated uric acid levels on arrival to the MICU in cases with sepsis are associated with poor prognosis and has increased risk for AKI, ARDS [8]. A study by Chuang CC *et al*. stated that uric acid levels are associated strongly with prevalent CKD. Because of progressive loss of GFR, patients with CKD have decreased renal clearance of uric acid and thus greater serum uric acid levels than the general population [2]. A study by Xialian Xu *et al*. stated that the Hyperuricemia group significantly exerted a higher risk of AKI compared to the controls and the study conclude that the measurement of serum uric acid levels may help in the early diagnosis of acute kidney disease [10]. A study by Yoshida H *et al.* concluded that the elevated serum uric acid level at dialysis initiation was associated risk factor with infection related mortality [11]. A study by Bagshaw SM *et al*. concluded that septic AKI is independently associated with higher odds of death and longer duration of hospitalization [12]. A study by Anand Srivastava *et al*. Concluded that plasma uric acid levels upon ICU admission or before RRT initiation are not independently associated with adverse clinical outcomes in critically ill patients [13].

Conclusion

The results of the study conclude that estimation of serum uric acid may be used as important predictor for the severity of the condition furthermore as predictor of mortality and morbidity in cases with clinically diagnosed sepsis. Study demonstrated that Hyperuricemia may be associated with poor clinical outcome in cases with sepsis admitted to MICU.

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