

Correlation of Serum Uric Acid Level with Morbidities and Mortality in Sepsis Patient and its Prognostic Significance

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Abstract

Introduction: Increased oxidative stress due to high oxygen free radicals and decreased antioxidants causes multi-organs failure, which includes kidney dysfunction, causing inhibition of uric acid (UA) excretion, resulting in rising serum UA. UA can be a marker of the severity of oxidative stress and poor prognosis in patients with sepsis.

Purpose: This study was conducted to find out the correlation or association between serum UA level with various morbidities and mortality in sepsis patient and its prognostic significance.

Materials and Methods: This was a prospective cohort study, conducted from March 2020 to August 2021 at tertiary care center in the state of Madhya Pradesh, India. The study includes 80 patients with the clinical diagnosis of sepsis in age group of ≥ 16 and ≤ 60 years of both sexes, who were admitted in the Department of Medicine. Clinical diagnosis of sepsis was based on 2016-Sepsis-3 criteria including quick-SOFA score. The patients were divided into two study groups: With serum UA level < 7 mg/dL and with serum UA level ≥ 7 mg/dL.

Results: It has been observed that cases with q-SOFA score-3 and serum UA level ≥ 7 mg/dL were having poor outcome (death) compared to cases with q-SOFA score-2 and serum UA level < 7 mg/dL. Cases with q-SOFA score-3 were observed to have positive association between pre-existing comorbidities at admission and their poor outcomes. Further observed that cases with the highest level of serum UA level ($> 9-12$ mg/dL) group have more chance of poor outcome. Cases with high UA value (≥ 7 mg/dL) have a longer duration of hospitalization and show a positive association between duration of hospitalization and serum UA level at admission.

Conclusion: Raised serum UA in sepsis patients at admission is associated with poor outcomes and longer hospitalization. Hence, in favorable condition, serum UA may serve as an early prognostic marker in sepsis patient at admission.

Key words: Outcome, Prognosis, q-SOFA score, Sepsis, Serum Uric Acid

INTRODUCTION

Uric acid (UA) is the end product of purine metabolism (through the action of xanthine dehydrogenase, and

xanthine oxidase) in humans. Purines are nitrogen-containing compounds. Most of the UA passed in urine. Some UA is degraded in the body after reaction with oxidants or peroxynitrite.^[1] Most of the studies which have been done suggest that raised UA has noted to be associated with atherosclerosis,^[2,3] hypertension (HTN), hyperinsulinemia,^[4] and chronic kidney disease.^[5]

Hyperuricemia is defined as accumulation of serum UA beyond its solubility point in water and develops due to UA overproduction, undersecretion, or both.^[6] UA can induce acute inflammation through UA crystals. UA

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crystals can induce pro-inflammatory cytokines, such as IL-1b, increase the production of reactive oxygen species, stimulate chemotaxis, and activate nuclear factor kappa B and mitogen-activated protein kinases pathways.^[7]

This study was conducted in patients coming to a tertiary care center in Jabalpur, Madhya Pradesh, India, who were admitted in the department of medicine ICU and Wards, with a clinical diagnosis of sepsis based on sepsis-3 criteria 2016 (quick SOFA criteria).

Hyperuricemia was defined more than 7 mg/dL in 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 (Systolic blood pressure [SBP] ≤ 100 mmHg), high respiratory rate (≥ 22 breaths/min), or altered mentation (glasgow coma scale < 15). 2–3 points indicate a high risk of poor outcome in patients with clinically suspected sepsis.

MATERIALS AND METHODS

Place of Study

This study carried out in the Department of Medicine, Netaji Subhash Chandra Bose Medical College and Hospital, Jabalpur in the state of Madhya Pradesh from March 2020 to August 2021.

Type of Study

The present study is a prospective cohort study.

Inclusion Criteria

The study includes 80 patients with the clinical diagnosis of sepsis in the age group of ≥ 16 and ≤ 60 years with both sexes who were admitted in Medicine wards, Emergency care unit in the Department of Medicine with the clinical diagnosis of sepsis based on 2016-Sepsis-3 criteria including q-SOFA score.

Exclusion Criteria

Who was age under 16 years and over 60 years, all pregnant females, patients from an outside facility in a medical intensive care unit for more than 24 h, patient with already known case of gout and chronic kidney disease, blood cancer like leukemia, patients already on hypouricemic or hyperuricemic drugs therapy, and HIV patient on anti-retroviral therapy were excluded from the study.

Procedures

Consent was taken after giving a proper description of the process to the patients. This study was accepted and confirmed by the Ethics Committee Netaji Subhash Chandra Bose Medical College and Hospital Jabalpur,

Madhya Pradesh, India. The epidemiological and clinical information of the patients was obtained by one physician and confirmed by another. UA level was measurement done by Machine-UA analyzer; Randox RX imola. The technique used was about 1.5 mL sample is centrifuged and put in the automatic analyzer machine and result is obtained in the central lab under the department of Biochemistry at Netaji Subhash Chandra Bose Medical College, Jabalpur. The patients were divided into two study groups: With serum UA level < 7 mg/dL and with serum UA level ≥ 7 mg/dL. Severity of sepsis was scored using q-SOFA Score. It uses three criteria, assigning one point for low blood pressure (SBP ≤ 100 mmHg), high respiratory rate (≥ 22 breaths/min), or altered mentation (Glasgow coma score < 15). 2–3 points indicate a high risk of poor outcome in patients with clinically suspected sepsis.

Outcome of the patient in the form of death and discharge were calculated, duration of their stay, a correlation or association between serum UA level with various morbidities in sepsis patient were measured.

Statistics

All data were entered into MS Excel 2007, analysis were done with the help of SPSS 23.0 software. Finally, relationship of the serum UA level was evaluated by the cutoff point of 7 mg/dL for each outcome. For comparison of the groups below 7 mg/dL UA group and ≥ 7 mg/dL UA, descriptive statistics such as mean and percentage were compared using Chi-square test, $P < 0.05$ was considered statistically significant.

RESULTS

- All the patients included in the study were above 16 years and < 60 years of the age. Among the 80 cases, 45 (56.3%) were male and 35 (43.8%) females in a mean age of 39.27 ± 13.50 years [Table 1].
- Out of total 80 cases, 4 (5.0%) cases were having UA < 7 mg/dL and 76 (95.0%) cases were having UA level ≥ 7 mg/dL [Table 2].
- Out of 80 cases, 28 (35.0%) were having q-SOFA score of 2 and 52 (65.0%) were having q-SOFA score of 3 [Table 3].
- Out of total 4 (5%) cases who were having serum UA level of < 7 mg/dL, patients with q-SOFA score of 2 were 1 (1.25%), all of which got discharged and with q-SOFA score of 3 were 3 (3.75%) cases, 2 (2.50%) cases died and 1 (1.25%) cases got discharged.
- Out of total 76 (95%) cases who were having serum UA level of more than equals to 7 mg/dL, patient with q-SOFA score of 2 were 27 (33.60%), out of which 11 (13.75%) cases died and 16 (20.00%) cases

Table 1: Sex wise distribution of case

Sex	Frequency	Percentage
Female	35	43.8%
Male	45	56.3%
Total No. of case (n=80)	80	100.0%

Table 2: Age wise distribution of case

Age group (in years)	Frequency	Percentage
≥16-20	6	7.5%
21-30	24	30.0%
31-40	15	18.8%
41-50	14	17.5%
51≤60	21	26.3%
Total No. of case (n=80)	80	100%

Table 3: Distribution of cases according to serum uric acid at admission

Serum uric acid at admission	Frequency	Percentage
<7 mg/dl	4	5.0%
≥7 mg/dl	76	95.0%
Total No. of cases (n=80)	80	100.0%

Table 4: Distribution according to q- SOFA score at admission

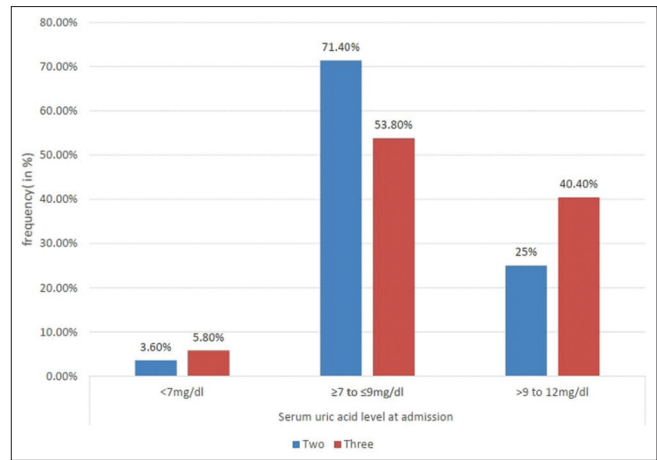
Q-SOFA score	Frequency	Percentage
2	28	35.0%
3	52	65.0%
Total No. of case (n=80)	80	100.0%

Table 5: Co-morbidities wise distribution of cases

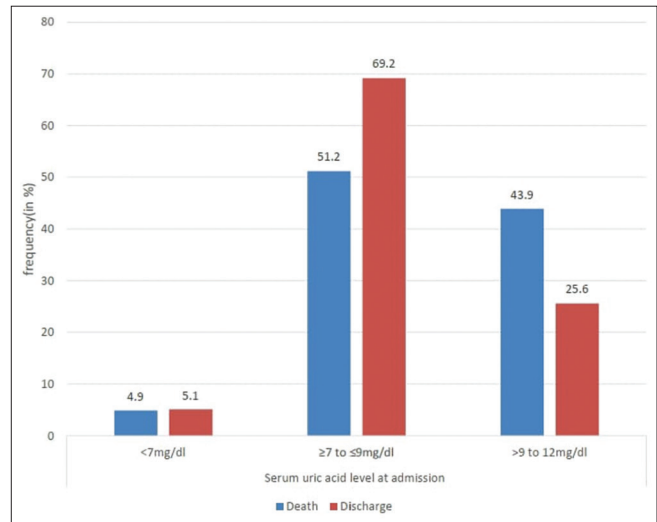
Comorbidity	Cases (n=80)	Percentage
Diabetes mellitus	14	17.50%
Hypertension	12	15%
IHD	7	8.75%
CVA/Meningitis	30	37.5%
COPD/Asthma	18	22.5%
Acute/Chronic liver disease	23	28.5%
AKI	20	25%
No co-morbidities	15	18.75%

got discharged and with q-SOFA score of 3 were 49 (61.25%) cases, out of which 28 (35%) cases died and 21 (26.25%) cases got discharged.

- Mean duration of hospital stay in serum UA < 7 mg/dL group was 3.85 ± 0.3 days and mean duration of hospitalization in serum UA ≥ 7 mg/dL group was 4.91 ± 4.61 days.
- Further we have subdivided the ≥7 UA group into ≥7–≤9 mg/dL and >9–12 mg/dL to see if there is actual association between severity of raised serum UA at admission with genders along with their q-SOFA



Graph 1: Relation of serum uric acid level and q-SOFA score at admission



Graph 2: Relation of serum uric acid level and their final outcome

score at admission and their final outcome. Out of total 28 cases with q-SOFA score of 2, 1 (3.60%) are in serum UA level <7 mg/dL group, 20 (71.40%) are in serum UA level ≥7–≤9 mg/dL group and 7 (25%) are in serum UA >9–12 mg/dL group [Graph 1].

- Out of total 52 cases with q-SOFA score of 3, 3 (5.80%) are in serum UA level <7 mg/dL group, 28 (53.80%) are in serum UA level ≥7–≤9 mg/dL group and 21 (40.40%) are in serum UA >9–12 mg/dL group [Graph 1].
- On comparing outcomes with serum UA, we observed that out of a total of 41 deaths that occurred, 2 (4.90%) were in serum UA level <7 mg/dL group, 21 (51.20%) were in serum UA level ≥7–≤9 mg/dL group and 18 (43.90%) were in serum UA >9–12 mg/dL group [Graph 2].
- Out of a total of 39 discharge that occurred, 2 (5.10%) were in serum UA level <7 mg/dL group, 27 (69.20%)

Table 6: Outcomes of cases with respect to q-sofa score at admission

Outcome	n=80 cases (100%)					
	Serum uric acid < 7 mg/dl (n ¹ =4) (5%)		Serum uric acid ≥ 7mg/dl (n ² =76) (95%)		Total	
	Q – SOFA score at admission					
	Score 2	Score 3	Score 2	Score 3	Score 2	Score 3
Death	0 (0.00%)	2 (2.50%)	11 (13.75%)	28 (35.00%)	11 (13.75%)	30 (37.50%)
Discharge	1 (1.25%)	1 (1.25%)	16 (20.00%)	21 (26.25%)	17 (21.25%)	22 (27.50%)
					28 (35.00%)	52 (65.00%)
Total No. of cases (n=80)		1 (1.25%)	3 (3.75%)	27 (33.60%)	49 (61.25)	80 (100%)
P value			0.248		0.172	

n = Total number of case in study, n¹=Number of cases with serum uric acid < 7, n²=Number of cases with serum uric acid ≥ 7.

Table 7: Correlations of duration of hospital stay of cases with level of serum uric acid at admission

Duration of hospital stay	Total cases n=80 cases	Serum uric acid <7 mg/dl at admission			Serum uric acid ≥7 mg/dl at admission			P value
		(n ¹ =4)	Death	Discharge	(n ² =76)	Death	Discharge	
≤1 Day	10	0	0	0	10	10 (100%)	0	-
>1 to ≤3 Days	29	0	0	0	29	13 (44.82%)	16 (55.17%)	-
>3 to ≤7 days	25	4	2 (8%)	2 (8%)	21	9 (36%)	12 (48%)	0.012
>7 days	16	0	0	0	16	7 (43.75%)	9 (56.25%)	-
Mean duration of stay	4.86±4.50 days	3.85±0.3 days	-	-	4.91±4.61 days	-	-	-

n=Total number of case in study, n¹=Number of cases with serum uric acid <7, n²=Number of cases with serum uric acid ≥7.

Table 8: Correlation of serum uric acid level at admission with genders, their q-SOFA score at admission and their final outcomes

Sample size	n=80 cases	4 (5%)			76 (95%)			P value
		<7 mg/dl			≥7 to ≤9 mg/dl			
Serum uric acid level at admission								
Male	45	2 (4.44%)	28 (62.2%)	15 (33.33%)				0.89
Female	35	2 (5.71%)	20 (57.14%)	13 (37.14%)				
Mean age (years)	39.27±13.50	45.8±13.3	36.5±13.4	43.1±12.9				-
Q-SOFA score								
2	28	1 (3.60%)	20 (71.40%)	7 (25%)				0.30
3	52	3 (5.80%)	28 (53.80%)	21 (40.40%)				
Death	41	2 (4.90%)	21 (51.20%)	18 (43.90%)				0.22
Discharge	39	2 (5.10%)	27 (69.20%)	10 (25.60%)				

were in serum UA level ≥7–≤9 mg/dL group and 21 (40.40%) were in serum UA >9–12 mg/dL group [Graph 2].

- The mean age of cases with serum UA level <7 mg/dL is 45.8 ± 13.3 years, with serum UA level ≥7–≤9 mg/dL is 36.5 ± 13.4 years and with serum UA >9–12 mg/dL is 43.1 ± 12.9 years [Table 4].

DISCUSSION

The present study was conducted in the Department of Medicine, Netaji Subhash Chandra Bose Medical College and Hospital, Jabalpur, in the state of Madhya Pradesh, India. In the present study out of 80 cases, 45 (56.3%) were male and 35 (43.8%) were females. Similar gender distribution was seen in a study done by Akbar et al. (2015)^[8] where in out of 144 cases, 83 (57.6%) cases were males and 61 (42.4%) cases were females.

In the present study, the average age of patients was 39.27 years. The distribution of cases in the age group ≥16–20 years, 21–30 years, 31–40 years, 41–50 years, and 51–≤60 years were 6 (7.5%), 24 (30.0%), 15 (18.8%), 14 (17.5%), 21 (26.3%), respectively. The majority of cases, that is, 24 (30.0%), cases were in the age group 21–30 years, followed by 21 (26.3%) cases in the age group 51–≤60 years [Table 5].

In the study done on 38 cases by Sukmawardhani et al. (2019).^[9] Maximum cases (28.9%) was in age group 50–59 year. This may be due to health awareness in the early age group population leading them to seek health facility early. In our study, second maximum number of cases are in age group 51–≤60 years this may be due to the presence of comorbidity in this age group which increases the risk of sepsis and its severity which necessitates them to seek health facility.

In the present study, out of a total of 80 cases, 4 (5.0%) cases were having UA of <7 mg/dl, and 76 (95.0%) cases

were having UA of ≥ 7 mg/dl. In the study conducted by Bhandary *et al.* (2019)^[10] out of 60 patients included in the study 31 (51.66%) were having serum UA ≤ 7 mg/dl and 29 (48.33%) were having serum UA > 7 mg/dl. This may be due to the inclusion of more sick patients and more number of cases with coexisting comorbidity at admission in the present study which increases the severity of sepsis. There are also more cases in the older age group in the present study and physiologically, UA plasma level increases with age.

Out of 80, that is, total cases in our study, 14 (17.50%) cases had diabetes mellitus (DM), 12 (15%) cases had HTN, 7 (8.75%) cases had ischemic heart disease (IHD), 30 (37.50%) cases had central nervous system (CNS) complications, 18 (22.50%) cases had asthma/COPD, 23 (28.50%) cases had acute/chronic liver disease, 20 (25%) cases had acute kidney injury (AKI) as co-morbidity. In the study conducted by Akbar *et al.* (2015)^[8] on 144 cases, there were 53 (36.8%) diabetes, 37 (25.7%) coronary artery disease, 24 (16.7%) CVA as comorbidities in case. Bhandary *et al.* (2019)^[10] found, out of 60 patients included in the study 4 (6.66%) have IHD, 14 (23.3%) have DM, 17 (28.33%) have HTN, 28 (46%) have AKI as comorbidities. These differences in the distribution of comorbidities in the cases may be due to differences in incidence and prevalence of disease and socioeconomic structure, in the study locality. It may be due to difference in gender and age in the study population and previous studies.

In this study, when comparing q-SOFA score in serum UA level < 7 and outcome at admission, out of 4 (5%) cases, 2 (2.50%) cases died and 2 (2.50%) discharged [Table 6], there was a positive association. Chi-square value was 1.33 and $P = 0.248$ which is statistically insignificant. When comparing q-SOFA score in serum UA level ≥ 7 and outcome at admission, out of 76 (95%) cases, in 39 (48.75%) death occurred and 37 (46.25%) cases got discharged [Table 7], there was a positive association between outcome and serum UA level at admission. Chi-square value was 1.875 and $P = 0.171$ which is statistically insignificant.

In the present study of 80 cases, a total of 41 deaths occurred, out of which 2 (4.87%) occurred in cases with UA level < 7 mg/dL and 39 (95.18%) deaths occurred in cases with serum UA ≥ 7 mg/dL. The similar results were seen in a study done by Bhandary *et al.* (2019),^[10] there were 10% death in cases with UA level < 7 mg/dL and 90% of death occurred in cases with serum UA ≥ 7 mg/dl.

In the present study, in the patient with low q-SOFA score (Score 2), the final outcome is good (the majority of the patients were discharged) and in patient who were

having higher q-SOFA score (score 3), the final outcome is poor (majority of the patient died). This may be due to higher q-SOFA score suggesting of higher severity of sepsis and organ dysfunction, leading to higher mortality in comparison to cases having lower q-SOFA scores. Further high free radicals and low levels of antioxidants in sepsis patients are believed to cause multiorgan failure, one of which is kidney dysfunction, which results in inhibition of UA excretion, causing raised UA.

In the present study, we have further classified hyperuricemia in two subgroups, that is, ≥ 7 – ≤ 9 mg/dl and > 9 – 12 mg/dl group to fulfill the secondary objective to establish that the actual increase in serum UA value as an early prognostic marker of morbidities and mortality outcome in sepsis patients during their hospital stay. In which out of 45 males, most, that is, 28 (62.2%) are in serum UA level ≥ 7 – ≤ 9 mg/dl group, in females out of 35, maximum, that is, 20 (57.14%) are in serum UA level ≥ 7 – ≤ 9 mg/dl group. $P = 0.30$ which is statistically not significant. The mean age of cases with serum UA level 9–12 mg/dl is 43.1 ± 12.9 years.

In the study conducted by Bhandary *et al.* (2019)^[10] in 60 cases, the mean age of cases with serum UA level < 7 mg/dl was 55.26 ± 13.8 years, with serum UA level ≥ 7 – ≤ 9 mg/dl was 53.59 ± 15 years and with serum UA > 9 – 12 mg/dl is 43.1 ± 12.9 years. The difference might be due to asymmetrical age distribution of cases in the present study and inclusion of more cases of older age in the other studies. In the present study, we found that most of the cases with high serum UA level have high q-SOFA score. $P = 0.89$ which is statistically not significant. When comparing outcomes with serum UA, we observed most patient with the highest serum UA group i.e. > 9 – 12 mg/dL group patient death is more than discharge. $P = 0.22$ is statistically not significant. The statistical not significance may be due to small sample size and also due to non-follow-up of discharge cases and needs further research.

In the present study, all the patients, that is, 10 who stayed for ≤ 1 day were in serum UA level ≥ 7 mg/dL, all died. It was observed that most of the cases who have longer duration of hospital stay were in group with serum UA level ≥ 7 mg/dL [Table 8]. There was a positive association between duration of hospitalization and serum UA level at admission, Pearson Chi-square = 10.94, $P = 0.012$ which is statistically significant.

Mean duration of hospital stay in serum UA < 7 mg/dl group was 3.85 ± 0.3 days and the mean duration of hospital stay in serum UA ≥ 7 mg/dl group was 4.91 ± 4.61 days [Table 8]. In the study conducted by Bhandary *et al.* (2019)

^[10] which included 60 cases, the mean duration of hospital stay in serum UA <7 mg/dL group was 2.16 ± 1.44 days and mean duration of hospital stay in serum UA ≥ 7 mg/dL group was 11.9 ± 5.9 days. A study conducted by Zhong *et al.* (2022)^[11] also confirmed that high serum UA levels were significantly associated with increased risk 90-day all-cause mortality and the incidence of AKI in sepsis patients in the ICU. A large-scale cohort study of seven years in Japan found that even a slight increase in serum UA levels is an independent risk factor for all cause and cardiovascular death in men and women.^[12] The difference might be due to asymmetrical age distribution of cases in the present study. The short duration of stay (≤ 1 day) in serum UA level ≥ 7 mg/dL and poor outcome might be explained as those who have high serum UA level have already developed multiorgan dysfunction leading to poor outcome in them or in those having longer duration of stay in serum UA ≥ 7 mg/dL group might be due to multiple organs dysfunction that have been occurred would have been taking longer time to recover to its normal state.

CONCLUSION

It would be concluded here, that in the present study, overall young male patients were more. After observation, we have found that cases with low serum UA level and high q-SOFA score have poor outcome in the form of death or prolonged hospital stay than cases having lower serum UA and low q-SOFA score. In the category of high serum UA with high q-SOFA score, there is poor outcome than cases with high serum UA with low Q-SOFA score. Most cases presented with CNS complication as comorbidity in the present study. The presence of pre-existing comorbidities further increase the severity, morbidity, and mortality in patient with sepsis in comparison to those cases who do not have any comorbidity at admission. In the group with high UA at admission, there was more death than discharge suggesting the level of serum UA at admission can be an early marker of poor outcome. The presence of high UA level, there is more cases having a longer duration of hospital stay suggesting high morbidity. Hence, the raised serum uric acid value in sepsis patients has a positive association with poor outcomes. It may be useful early marker for further determining prognostic value in sepsis

patient at admission. However, further case–control study will be required to establish this hypothesis.

Limitation of the Study

The statistical insignificance if any in the above study was probably attributable to the small cohort under study and the short duration of follow-up. This was a single-center study within our limited resources.

Ethical Issues

The present study work had been done in the Department of Medicine at Netaji Subhash Chandra Bose Medical College and Hospital, Jabalpur, Madhya Pradesh, India. The study work has been approved by the Institutional Ethics Committee.

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