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HYPERURICEMIA AS AN EARLY MARKER IN PREDICTING MORBIDITY AND MORTALITY IN PATIENTS WITH SEPSIS

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Abstract

Sepsis is a life-threatening condition characterized by a dysregulated immune response to infection, leading to organ dysfunction. This study investigates the role of hyperuricemia as an early predictor of morbidity and mortality in sepsis patients. Conducted at Government Vellore Medical College & Hospital, this study analyzed the relationship between elevated serum uric acid levels and sepsis outcomes, including acute kidney injury, acute respiratory distress syndrome, and length of stay in the ICU. The findings suggest that hyperuricemia is a significant prognostic marker for adverse outcomes in sepsis.

Aims-

To analyse hyperuricemia as an early marker in predicting the morbidity and mortality in patients with sepsis. To find out the correlation between hyperuricemia and severity of sepsis in clinically suspected sepsis patient

Introduction- Sepsis, a severe medical condition triggered by the body's extreme response to infection, can lead to organ dysfunction and death if not promptly treated. The pathophysiology involves a complex interplay of pro-inflammatory and anti-inflammatory responses, oxidative stress, and endothelial dysfunction. Recent studies have highlighted the potential of serum uric acid as a prognostic marker for sepsis due to its role in oxidative stress and systemic inflammation.

Methods- This observational study included patients diagnosed with sepsis based on the quick Sequential Organ Failure Assessment (qSOFA) score admitted to the ICU. Hyperuricemia was defined as serum uric acid levels >7 mg/dL. Data on patient demographics, clinical parameters, serum uric acid levels, and outcomes were collected and analyzed.

Results- The study conducted at the Department of General Medicine, MGM, aimed to investigate hyperuricemia as a potential early marker for predicting morbidity and mortality in sepsis patients. Out of the 200 patients studied, a significant majority (66%) were aged over 45 years, with a mean age of 66.2 years. The gender distribution was nearly equal. Common comorbidities observed included diabetes mellitus (30 patients), hypertension (29 patients), and cardiac diseases (24 patients). Clinical parameters revealed that patients typically presented with an average respiratory rate of 25.4 per minute, mean arterial pressure of 65.9 mmHg, and systolic blood pressure of 91.4 mmHg. Fever was prevalent (mean temperature 38.7°C), and neurological impairment, as assessed by the Glasgow Coma Scale, indicated sepsis-related encephalopathy in 61.5% of cases. Laboratory findings showed elevated inflammatory markers with a mean C-reactive protein level of 43.46 mg/dl and a mean serum uric acid level of 7.44 mg/dl. Patients were stratified based on qSOFA scores, revealing 75 with sepsis, 47 with severe sepsis, and 78 in septic shock. Significant associations were found between serum uric acid levels and qSOFA scores ($p = 0.0021$), as well as a strong positive correlation between qSOFA scores and uric acid levels ($r = 0.46$, $p = 0.001$). Moreover, there was a notable difference in mean hospital stay durations across sepsis severities, with septic shock patients staying an average of 21 days compared to 15 days for severe sepsis and 11 days for sepsis. Although higher levels of uric acid were observed in patients who did not survive, this difference did not reach statistical significance in predicting mortality. These findings underscore the potential utility of serum uric acid as a marker in assessing severity and prognosis in sepsis, warranting further investigation into its clinical implications.

Conclusion- Hyperuricemia serves as an early marker for predicting morbidity and mortality in sepsis patients. Incorporating serum uric acid measurement into the clinical management of sepsis could enhance prognostic accuracy and improve patient outcomes.

Keywords- Sepsis, Hyperuricemia, Prognostic marker, Morbidity, Mortality.

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 8, 2024

INTRODUCTION

Sepsis is a life-threatening condition that happens when the body's immune system has an extreme response to an infection, causing organ dysfunction (1). The body's reaction causes damage to its own tissues and organs and it can lead to shock, multiple organ failure and sometimes death, especially if not recognized early and treated promptly.

Sepsis can affect anyone, but people who are older, very young, pregnant or have other health problems are at higher risk.(2)

Common signs of sepsis include fever, increased heart rate, Tachypnea, confusion and body pain. It can lead to septic shock which may result in multiple organ failure and death.

Sepsis is usually caused by bacterial infections but may be the result of other infections such as viruses, parasites or fungi. Its treatment requires medical care, including the use of antimicrobials, intravenous fluids and other measures.(3)

Over the last two decades, studies have demonstrated that infections can lead to the malfunctioning of several organs without causing a detectable inflammatory excess, that is, without eliciting the systemic inflammatory response syndrome (SIRS). In actuality, there are notable alterations in other pathways as well as pro- and anti-inflammatory reactions. The Sepsis Definitions Task Force presented the Third International Consensus Definitions in 2016 to update terminology and reflect current knowledge of the pathobiology of sepsis. This definition states that sepsis is a dysregulated host response to infection that results in acute organ failure.Septic shock is a consequence of sepsis that causes disruptions in the body's metabolic and circulatory systems.

In animals, purine metabolism results in allantoin, whereas in humans, it results in uric acid. One can have endogenous or exogenous purines. Purines are nitrogenous substances that are present in both diet and the body. The majority of uric acid is expelled in urine after passing through the liver and into the bloodstream[4]. Following an interaction with oxidants, the body breaks down some uric acid . Normal levels of blood uric acid are typically 3.4–7.2 mg/dL for men and 2.4–6.1 mg/dL for women. Strong correlations between uric acid and atherosclerosis[5], hypertension, hyperinsulinemia[6], and chronic renal disease [7] have been discovered during the past ten years.

Through uric acid crystals, uric acid can cause acute inflammation of the renal epithelial cells. Due to its noncrystal properties, uric acid can also have an influence on the human body. By activating the renin-angiotensin-aldosterone system [8], activating various inflammatory transcription factors [9], inducing systemic cytokine production such as tumor necrosis factor alpha [10], and inducing local expression of chemokines such as monocyte chemotactic protein 1 in the kidney and cyclooxygenase 2 (COX-2) in blood vessels [11], it may cause endothelial dysfunction, an afferent renal arteriolopathy, and tubulointerstitial fibrosis in the kidney. Reduced urine nitrite levels and systemic and glomerular hypertension are the results of experimentally induced hyperuricemia in rats [12,13].

Uric acid reduces the formation of nitric oxide [14] and may cause nitric oxide depletion [15]. Uric acid reacts directly with Nitric oxide in a Rapid Irreversible reaction resulting in formation of 6-aminouracil and depletion of Nitric Oxide, Reduction in endothelial cell NO level leads to "endothelial Dysfunction" which has been identified as a key pathogenic event preceding development of Hypertension, Metabolic Syndrome and other Cardiovascular Disease[54]. Because urate is a potent antioxidant at physiological quantities that can scavenge superoxide, hydroxyl radicals, and singlet oxygen, the noncrystal effects of uric acid are still controversial [16-18].

Higher serum uric acid is a poor prognostic indicator for sepsis patients because it can lead to multi-organ failure from higher oxygen free radicals. This is how oxidative stress is identified.Serum uric acid levels that are elevated are indicative of a bad prognosis in individuals with severe infections because they cause rapid activation of several transcription factors. Serum uric acid elevation is also linked to chronic diseases.[19,20]

Therefore, the purpose of this study was to determine the relationship between hyperuricemia in patients with clinically diagnosed sepsis and morbidity and mortality. Additionally, the study aimed to determine the relationship between hyperuricemia in sepsis patients and acute kidney injury, ARDS, and length of stay in patients receiving medical intensive care. Patients who were admitted to the intensive care unit (ICU) with a

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clinical diagnosis of sepsis based on a

MATERIAL AND METHODS:
Necessary permission was taken from

The Ethical Committee
Research Review Board

- Type of Study: Hospital based observational study
- Study design: Prospective study
- Period of Study: From June 2022 to December 2023
- Place of Study: Mahatma Gandhi Medical College & Hospital, Jaipur
- Written and informed consent of the patients was obtained from all participants before enrolment into the study.
- Sample size calculation- Sample size was calculated using Epi Info Software at 5 % Confidence Interval using article of Naomi et al [71], where the total population was 680 and prevalence of sepsis was 56.4%.
  Hence the calculated size was 191 at 10% error. To drop out the failure we rounded of the sample size to 200.

SELECTION OF CASES:
All cases of Sepsis

INCLUSION CRITERIA-
1. Pt who gave written consent.
2. ≥ 18 yr age group of both sex
3. Sepsis suspected with qSOFA CRITERIA

EXCLUSION CRITERIA-
1. Patients (age<18 years and >80 years old) of first hospitalization
2. Patients who were diagnosed to have gout
3. Chronic renal failure
4. Malignancy
5. All pregnant females
6. Patients on diuretics were excluded.

fast SOFA score participated in the study, which was carried out at Mahatma Gandhi Medical College and Hospital, Jaipur, a tertiary care facility. For both males and females, hyperuricemia was classified as >7 mg/dl[13]. For both males and females, an absolute rise in creatinine over the baseline of >0.3 mg/dl was considered acute renal damage.

Statistical Analysis:
Data collected was analysed by frequency, percentage, mean, standard deviation (S.D).Appropriate statistical tests was used to find significant association. P Value < 0.05 was considered statistically significant.

CORRELATION was calculated using Pearson's coefficient.

TABLE 1-AGE WISE DISTRIBUTION OF THE PATIENTS WITH SEPSIS UNDER STUDY

AGE GROUP (YEARS)	NUMBER	PERCENTAGE(%)
18-30	22	11
31-45	45	22.5
46-60	61	30.5
>60	72	36
TOTAL	200	100

In our study approximately 66% pts belonged to >45 yr age group. Very less i.e. 11% pts belonged to 18-30 year age group.The mean age of the study patients was 66.2±20.01 years

TABLE 2- SEX WISE DISTRIBUTION OF THE PATIENTS WITH SEPSIS UNDER STUDY

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 8, 2024

SEX	NUMBER	PERCENTAGE (%)
MALE	101	50.5
FEMALE	99	49.5
TOTAL	200	100

In our study males and females were almost equal.

TABLE 3- COMORBIDITIES IN THE PATIENTS WITH SEPSIS UNDER STUDY

COMORBIDITIES	NUMBER	PERCENTAGE(%)
DM	30	15
HTN	29	14.5
CARDIAC DISEASES	24	12

In our study 30 pts had DM, 29 had HTN and 24 had cardiac diseases.

TABLE 4- VARIABLES IN THE PATIENTS WITH SEPSIS UNDER STUDY

VARIABLES	MEAN	SD
RESPIRATORY RATE (/min)	25.4	4.3
PULSE RATE (/min)	102.9	18.9
TEMPERATURE (^{0}c)	38.7	0.91
SYSTOLIC BLOOD PRESSURE (SBP) (/mmHg)	91.4	21.3
MEAN ARTERIAL PRESSURE (MAP)	65.9	18.7
GLASSGOW COMMA SCALE (GCS) (3-15)	13.7	1.58
SEPSIS ASSOCIATED ENCEPHALOPATHY, n (%)	123(61.5%)	-

The vital data in our research were documented as- The average respiratory rate was 25.4 per minute. The mean arterial pressure (MAP) measured 65.9 millimeters of mercury (mmHg), and the systolic blood pressure was 91.4 mmHg. Fever was the predominant condition among the patients included in the study, with the mean temperature recorded at 38.7°C. The patients' level of consciousness was evaluated using the Glasgow Coma Scale (GCS), and the average score was 13.7. Sepsis-related encephalopathy was detected in 123 out of the total studied patients, representing 61.5%.

TABLE5- LABORATORY PARAMETERS IF THE PATIENTS WITH SEPSIS UNDER STUDY

LABORATORY PARAMETERS	MEAN	SD
WBC (*10^6/l)	16.73	11.5
Hb (mg/dl)	10.11	2.32
ESR (mm/hr)	67.3	41.2
PLT (*109/l)	193.2	41.56
CRP (mg/dl)	43.46	42.9
ALT (U/l)	66.7	61.9
AST (U/l)	71.9	81.3
DIRECT BILIRUBIIN (mg/dl)	1.03	0.91
INDIRECT BILIRUBIN (mg/dl)	1.13	1.05
SERUM URIC ACID (mg/dl)	7.44	3.17

Alt- Alanine Transaminase, Ast-Aspartate Tranaminase, Anc- Absolute Neutrophil Count, Crp- C Reactive Protein, Esr- Erythrocyte Sedimentation Rate, Hb- Hemoglobin, Plt- Platelet, Wbc- White Blood Cells.

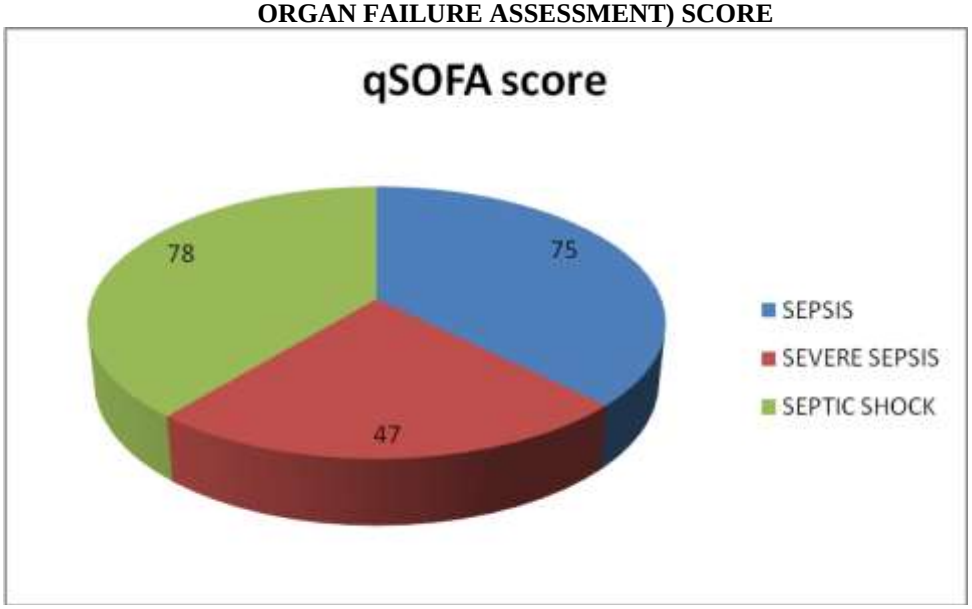
The mean total leukocyte count in the studied population was 16.73 *106/l. Indirect bilirubin was measured at 1.13 mg/dl, alanine transaminase at 66.7 Ul/l, and aspartate transaminase at 71.9 Ul/l. The mean C-reactive protein level was 43.46 mg/dl, indicating sensitivity to inflammation related to sepsis. Erythrocyte sedimentation rate had a mean of 67.3 mm/h, while the mean hemoglobin level was 10.11 mg/dl. The average platelet count was 193.2*109/l, and the mean serum UA, a key laboratory parameter in this study, was 7.44 mg/dl.

TABLE 6- CLASSIFICATION OF THE PATIENTS ACCORDING TO qSOFA (SEQUENTIAL ORGAN FAILURE ASSESSMENT) SCORE

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 8, 2024

qSOFA SCORE	NUMBER	PERCENTAGE (%)
SEPSIS	75	37.5
SEVERE SEPSIS	47	23.5
SEPTIC SHOCK	78	39
MEAN SCORE	6.52±2.9	

GRAPH 6-CLASSIFICATION OF THE PATIENTS ACCORDING TO qSOFA (SEQUENTIAL ORGAN FAILURE ASSESSMENT) SCORE



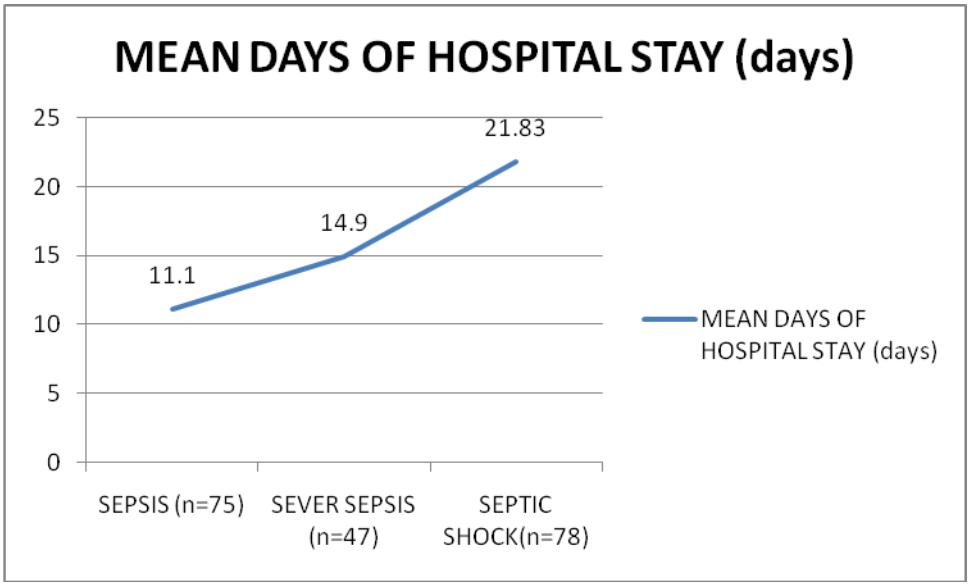
Among the studied patients, 75 patients categorized as sepsis according to the qSOFA score, while 47 patients were categorized to have severe sepsis and finally 78 patients were in septic shock state.

TABLE 7-MEAN DAYS OF HOSPITAL STAY ACCORDING TO QSOFA SCORE

	SEPSIS (n=75) mean±SD	SEVER SEPSIS (n=47) mean±SD	SEPTIC SHOCK(n=78) mean±SD	TEST OF SIGNIFICANCE	P VALUE	P 1 VALUE	P 2 VALUE	P 3 VALUE
MEAN DAYS OF HOSPITAL STAY (days)	11.1±3.9	14.9±2.91	21.83±3.65	0.021	0.001	0.031	0.035	0.1557

GRAPH 7-

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 8, 2024



Mean days of hospital stay stated significant difference according to severity of sepsis. Septic shock pts had mean days of hospital stay of approx 21 days , followed by 15 days in severe sepsis and 11 days in sepsis.

TABLE 8- LEVEL OF SERUM URIC ACID IN DIFFERENT LEVELS OF SEPSIS IN PATIENTS UNDER STUDY

	SEPSIS (n=75) mean±SD	SEVER SEPSIS (n=47) mean±SD	SEPTIC SHOCK(n=78) mean±SD	TEST OF SIGNIFICANCE	P VALUE	P 1 VALUE	P 2 VALUE	P 3 VALUE
SERUM URIC ACID	6.0±2.6	7.7±2.6	7.83±3.65	0.5	0.0021	0.007	0.0022	0.86

P1, comparison between tertiles 1 and 2; P2, comparison between tertiles 1 and 3; P3, comparison between tertiles 2 and 3

As regards qSOFA score, significance was found between serum UA and score (*P*;0.0021).

TABLE 10- CORELATION BETWEEN QSOFAAND LABORATORY PARAMETERS

	R (PEARSON's CORRELATION COEFFICIENT)	P value
DIRECT BILIRUBIN	0.1	0.1
INDIRECT BILIRUBIN	0.2	0.8
SERUM URIC ACID	0.46	0.001

There was strong correlation found between qSOFA Score and uric acid

DISCUSSION

Sepsis is a severe immune response to infection, potentially leading to organ dysfunction and mortality if not promptly treated. It can affect anyone but poses greater risks to vulnerable demographics such as the elderly, young children, pregnant women, and those with underlying health issues.

Clinical signs of sepsis include fever, elevated heart rate, rapid breathing (Tachypnea), confusion, and body pain. If untreated, it can progress to septic shock, causing multiple organ failure and death. While bacterial infections are the primary cause, sepsis can also stem from viral, parasitic, or fungal sources. Treatment necessitates medical intervention with antimicrobial drugs, intravenous fluids, and supportive care.

Recent research, including the Third International Consensus Definitions from 2016, highlights that sepsis is characterized by a dysregulated host response to infection, resulting in acute organ failure. This understanding has evolved beyond the traditional systemic inflammatory response syndrome (SIRS) criteria, recognizing various immune and inflammatory pathways involved.

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 8, 2024

Uric acid, a byproduct of purine metabolism, plays a controversial role in health and disease. Elevated serum uric acid levels, often observed in conditions like sepsis, have been linked to worsened outcomes due to increased oxidative stress. Uric acid can trigger inflammation through various mechanisms, including the activation of inflammatory transcription factors and the induction of systemic cytokine production.

In patients with sepsis, hyperuricemia (>7 mg/dL) has been associated with higher morbidity and mortality rates. It contributes to acute kidney injury (AKI), acute respiratory distress syndrome (ARDS), and prolonged ICU stays. This relationship underscores the importance of monitoring and managing uric acid levels as part of sepsis management protocols.

At Mahatma Gandhi Medical College and Hospital in Jaipur, a study was conducted focusing on the impact of hyperuricemia on sepsis outcomes. Patients admitted to the ICU with sepsis, as determined by a fast SOFA score, were included. Elevated uric acid levels correlated with worse prognoses, including increased oxidative stress and multi-organ failure. The study highlighted the need for interventions targeting uric acid levels to potentially improve patient outcomes.

In conclusion, while sepsis remains a critical medical emergency, understanding its complex pathophysiology, including the role of uric acid, is crucial for developing effective treatment strategies. Monitoring and managing uric acid levels may offer a promising avenue for improving outcomes in septic patients, particularly in mitigating organ dysfunction and reducing mortality rates associated with this life-threatening condition.

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ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 8, 2024

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