ISSN: 0975-3583,0976-2833 VOL15, ISSUE 1, 2024

Original Research Article

Hyperuricemia-an Early Severity Marker of Sepsis in IMCU Patients

Dr. N. Bhargavi Sindhuja[1], Dr. P. Suganya[2], Dr. S. Sudha[3]

[1]Assistant Professor, Department of General Medicine, Government Kilpauk Medical College Hospital, Chennai, Tamil Nadu, India.

[2]Assistant Professor, Department of General Medicine, Government Kilpauk Medical College Hospital, Tamil Nadu, India.

[3]Assistant Professor, Department of General Medicine, Government Kilpauk Medical College Hospital, Tamil Nadu, India.

Corresponding Author

Dr. P. Suganya, Assistant professor, Department of General Medicine, Government Kilpauk Medical College Hospital, Chennai, Tamil Nadu, India.

Received: 09-12-2023 / Revised: 14-12-2023 / Accepted: 12-01-2024

ABSTRACT

Background

Majority of intensive care unit patients with Sepsis undergo ischemic- reperfusion injury and inflammation to varying degrees during their hospitalization. Uric acid may be a factor playing a role in these processes since it has both oxidant and antioxidant properties. Since high levels of oxyradicals and lower antioxidant levels in patients with sepsis are believed to result in multi organ failure,

Objective

hence we intend to measure uric acid levels as a marker of oxidative stress in patients with sepsis.

Methods

In this prospective study spanning over 12 months, 75 patients admitted in Intensive medical care unit who were more than 18 years old, with a clinical diagnosis of sepsis based on the quick SOFA (qSOFA), within the first 24 hours of IMCU admission were enrolled. Known case of kidney disease, gout or were on drugs causing hyperuricemia were excluded.

Results

The median age of the study group was 55.37 years in the study population, 56% of the patients belonged to 30-65 years age group. About 42.7% of the study population with sepsis had hyperuricemia (uric acid>7mg/dl). Among the hyperuricemia patients, 75% developed AKI; 40.6% developed ARDS and 81.25% of them had prolonged duration of stay (>72 hours).

Conclusion

This study demonstrates that Hyperuricemia can be potentially used as a marker of severity of illness as well as predictor of morbidity in patients with clinically diagnosed sepsis in the IMCU.

Keywords: Uric acid, Intensive Care Unit, sepsis severity.

Introduction

Sepsis is a serious medical condition characterized by a whole-body inflammatory state (systemic inflammatory response syndrome) and the presence of a known or suspected infection that has severe consequences. Hence majority of intensive care unit patients

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 1, 2024

undergo ischemic-reperfusion injury and inflammation to varying degrees during their hospitalization[1].

Risk factors for the progression from infection to organ dysfunction are not well understood, but may include underlying health status, organ function prior to infection, and timeliness of treatment. Age, sex, and race/ethnicity influence the incidence of sepsis, which is highest at both younger and older age groups, higher in males than females, and higher in blacks than whites. The difference in risk of sepsis by race is not fully explained by the socioeconomic factors or access to health care, raising the possibility that other factors, such as genetic differences among individuals in susceptibility to infection or in expression of proteins necessary for the host response, may play a role[1]. It has been shown that early initiation of treatment in sepsis has reduced the morbidity and mortality resulting from infection[2].

Uric acid passes through the liver, enters the blood stream and most of it excreted in urine[3]. Oxidative stress is a poor prognostic sign in case of patients with sepsis as multi organ[3] dysfunction occurs as a result of high oxygen free radicals[4,5]. 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. Strong association has been found for elevated serum uric acid levels with atherosclerosis[6,7], hypertension, hyperinsulinemia[8,9] and chronic kidney disease[10]. Chronic conditions are also associated with elevated serum uric acid.

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, ARDS and duration of stay in medical intensive care patients.

MATERIALS AND METHODS

This was a prospective study with Patient enrolment spanning 12 months from September 2018 – August 2019, All consecutive patients who were eligible based on the inclusion criteria of more than 18 years old and admitted in the IMCU with a clinical diagnosis of sepsis based on the quick Sequential Organ Failure Assessment (qSOFA)[11] score and after obtaining necessary consent - except for pregnant females, known case of kidney disease, patients who have already been in IMCU in an outside facility for more than 24 hrs , known case of gout and patients on drugs causing hyperuricemia,- were enrolled for this study. Ethical committee clearance was got from Institutional Ethical Committee of our hospital (Ref.No.010/ME1/2018).

75 patients who were qSOFA score based on three parameters; glasgow coma scale, systolic blood pressure and respiratory rate, assigning one point each to: Low blood pressure SBP <= 100 mmHg; High respiratory rate (>=22 breaths per minute) and GCS <15 were studied.

Clinical proforma for the study including demography was meticulously collected from the study participants. History of comorbidities such as Diabetes mellitus (Type I and II),Cerebrovascular accident, Tuberculosis, Malignancy, Mental retardation were collected. Basic vitals at admission heart rate, respiratory rate, blood pressure, oxygen saturation were recorded. Thorough general and systemic examination performed.

Blood samples were then obtained for uric acid, urea, creatinine, complete blood count, serum electrolytes and chest x-ray was taken. The patient’s creatinine at admission to IMCU was taken as the baseline value. Hyperuricemia was defined as value more than 7 mg/dl in males and females. Parameters such as requirement of mechanical ventilation, Acute kidney injury (as defined by KDIGO), Acute respiratory distress syndrome and duration of

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 1, 2024

stay in the IMCU were noted. Outcome of the sepsis event was classified as either death or discharge from the intensive care unit.

RESULTS

In this study population, the median age was 55.37 years with 56% belonged to 30-65 years age group; 52% were males and only 36% had no comorbidities. This has been depicted in the table 1.

Table 1: Demographic profile of study participants (n=75)

Variable	Category	Number	Percentage	P value
Gender	Male	39	52	0.351
	Female	36	48	
Age Group	< 30years	5	6.7	0.992
	30-65 years	42	56	
	>65 years	28	37.3	
Co-Morbidity	Type II Diabetes Mellitus	32	42.7	
	Decompensated Liver disease	4	5.3	
	Type I Diabetes Mellitus	3	4	
	Mental retardation	3	4	
	Systemic Hypertension	2	2.7	
	Cerebro vascular Accident	2	2.7	
	Tuberculosis	1	1.3	
	NO Co-morbidities	27	36	

Among the 75 study participants, 32 had elevated uric acid levels (>7 mg/dl) which constitutes about 42.7%,(95% Confidence Interval= 31.21% - 54.12%) whereas 43 patients constituting 57.3% had normal uric acid levels.

61% succumbed to sepsis while the remaining got discharged. 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. (Table 2)

Table 2: Frequency of the study variables (n=75)

Variable	Categories	Number	Percentage
Uric Acid	(Hyperuricemia) ≥7	32	42.7
	< 7	43	57.3
Duration of stay in ICU (Intensive care Unit)	> 72 hrs	41	54.7
	≤ 72 hrs	34	45.3
Complications	AKI	29	38.7
	ARDS	15	20.0
	AKI & ARDS	09	12.0
	Nil Complications	22	29.3
Outcome	Death	46	61.3
	Discharged Alive	29	38.7

This study aims at understanding the correlation between hyperuricemia and the prolonged duration of stay in hospital. Among patients with hyperuricemia, 81.25% required intensive care for more than 72 hours and the other way, among the patients who stayed in the intensive care for >72 hours, 63.41% had elevated Uric acid levels. 34.88% of patients with

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 1, 2024

normal uric acid levels required intensive care stay for more than 72 hours. Majority of the hyperuricemic patients among sepsis study population had prolonged duration of stay in hospital which signifies increased morbidity. (Table 3)

One of the end points of this study is the outcome of patients status with regards to sepsis and its relation to hyperuricemia. In this study, it was found that out of the 32 patients with hyperuricemia, 23 had expired which constitutes 71.9% and 9 were discharged which is 28.1%. However, this was not statistically significant (p=0.151).

On correlating hyperuricemia with occurance of complications like AKI & ARDS, AKI was significantly higher in the hyperuricemia group. 75% of the septic patients with hyperuricemia developed AKI. The percentage of septic patients with normal uric acid levels developing AKI was 32.5%. Also, among the patients who developed AKI, 58.6% had hyperuricemia and 41.4% had normal uric acid levels. Similarly, 40.6% of patients with hyperuricemia developed ARDS whereas it was only 25.5% in the normal uric acid levels group. p value was found be statistically significant with a value of <0.001. (Table3)

In this study, 32 patients were on mechanical ventilation in the intensive care unit. This constituted to 42.7% of the study population. Sepsis patients developing ARDS were 24 in number within the study population. Out of which, 20 patients were mechanically ventilated (83.3%). The correlation between mechanical ventilation and complications in the patients was found to be statistically significant (p value <0.001).

Table 3: Association of Study Variables with Hyperurecemia (n=75)

		n	Hyperuricemia	p value
Age Group	<30 years	5	2 (40.0%)	0.992
	30-65 years	42	18 (42.9%)	
	> 65 years	28	12 (42.9%)	
Gender	Male	39	19 (48.7%)	0.351
	Female	36	13 (36.1%)	
Duration of stay in ICU	> 72 hrs	41	**26 (63.4%)**	<0.001*
	≤ 72 hrs	34	06 (17.7%)	
Complications	AKI	29	17 (58.6%)	<0.001†
	ARDS	15	06 (40.0%)	
	AKI & ARDS	09	07 (77.8%)	
	Nil Complications	22	***02 (09.1%)***	
Outcome	Death	41	**23 (56.1%)**	0.151
	Discharged Alive	34	09 (26.5%)	

***-Chi Square test; † Fischer's Exact**

DISCUSSION

In this 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 defence 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[12]. And any resultant 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[13,14]

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[15,16] and hence uric acid is believed to be an important marker of oxidative stress.

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 1, 2024

The mechanisms for increased uric acid are not well understood. 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 microvascular endothelium[17,18]. When there is accumulation and deposition of Uric acid in the blood vessels, the release of vasorelaxation factors is hampered[4], 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

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

Usually the patients with sepsis are a very complex subset of population who have MODS and bad prognosis and are usually very sick patients. Hemodynamic changes, changes in the functional capacity of the heart and liver, exposure to multiple medications and numerous other factors causes development of AKI in these patients. Among these factors, uric acid can also contribute to development of AKI. The mechanism by which uric acid causes AKI can range from indirect injury secondary to the release of vasoactive mediators and oxidative stress to crystal induced direct tubular toxicity. Uric acid induced renal vasoconstriction due to catecholamine release activation of renin-angiotensin system, release of pro-inflammatory markers, oxidative stress and decreased nitric oxide levels, in turn causes AKI.

Nitric oxide release of endothelial cells is profoundly decreased by uric acid[19]. Khosla et al. [20] have revealed a decrease in plasma nitrites (metabolites of NO) in rats with hyperuricemia by allopurinol. Zoccali et al.[21] have demonstrated a correlation between high uric acid levels and dysfunction of endothelium[22]. Various pro-inflammatory markers such as MCP and CRP are increased as a response to inflammation induced by uric acid. Uric acid stimulates an inflammatory response via increasing various pro-inflammatory markers such as MCP and CRP.

In spite of having both antioxidant and oxidative properties, it appears that in periods of significant degrees of stress such as sepsis uric acids' protective antioxidative properties[23] get overwhelmed and that despite increased levels of oxidative stress leading to increased uric acid levels the uric acid is more injurious than beneficial to the human body. Hence uric acid may be an early marker of impending AKI in patients with sepsis and could be used to predict the risk for AKI in sepsis patients

The second 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.

Thus raising thoughts that will treatment of hyperuricemia improve patient outcomes and decrease length of stay in the IMCU? 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 but was shown by Aljmor et al[24]. Thus although uric acid levels may be used to predict the severity of illness, duration of stay in IMCU, 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.[25] to correlate with clinical severity of primary pulmonary hypertension and has an independent

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 1, 2024

association with long-term mortality of patient with primary pulmonary hypertension. This was most likely due to the small sample size. 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

This study demonstrates that 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 cohort with matched controls to confirm the observations.

REFERENCES

1. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992 Jun;101(6):1644-55.
2. Wawrzeniak IC, Loss SH, Moraes MC, De La Vega FL, Victorino JA. Could a protocol based on early goal-directed therapy improve outcomes in patients with severe sepsis and septic shock in the Intensive Care Unit setting?. Indian J Crit Care Med 2015; 19 (3):159-165.
3. Doehner W, Schoene N, Rauchhaus M, et al. Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: results from 2 placebo-controlled studies. Circulation. 2002 Jun 4;105(22):2619-24.
4. Edwards NL. The role of hyperuricemia and gout in kidney and cardiovascular disease. Cleveland Clinic journal of medicine. 2008 Jul 1;75(5):S13.
5. Ioachimescu AG, Brennan DM, Hoar BM, Hazen SL, Hoogwerf BJ. Serum uric acid is an independent predictor of all-cause mortality in patients at high risk of cardiovascular disease: a preventive cardiology information system (PreCIS) database cohort study. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. 2008 Feb;58(2):623-30.
6. Patetsios P, Rodino W, Wisselink W, Bryan D, Kirwin JD, Panetta TF. Identification of Uric Acid in Aortic Aneurysms and Atherosclerotic Artery. Annals of the New York Academy of Sciences. 1996 Nov;800(1):243-5.
7. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality: the NHANES I epidemiologic follow-up study, 1971-1992. Jama. 2000 May 10;283(18):2404-10.
8. Nakagawa T, Cirillo P, Sato W, et al. The conundrum of hyperuricemia, metabolic syndrome, and renal disease. Internal and emergency medicine. 2008 Dec 1;3(4):313-8.
9. Hunsicker LG, Adler S, Caggiula A, et al. Modification of Diet in Renal Disease Study Group. Predictors of the progression of renal disease in the Modification of Diet in Renal Disease Study, Kidney international. 1997 Jun 1;51(6):1908-19.
10. Iseki K, Oshiro S, Tozawa M, Iseki C, Ikemiya Y, Takishita S. Significance of hyperuricemia on the early detection of renal failure in a cohort of screened subjects. Hypertension Research. 2001;24(6):691-7.

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 1, 2024

11. Badrinath K, Shekhar M, Sreelakshmi M, et al. Comparison of various severity assessment scoring systems in patients with sepsis in a tertiary care teaching hospital. Indian J Crit Care Med 2018; 22 (12):842-845.
12. Cowley HC, Bacon PJ, Goode HF, Webster NR, Jones JG, Menon DK. Plasma antioxidant potential in severe sepsis: a comparison of survivors and nonsurvivors. Critical care medicine. 1996 Jul 1;24(7):1179-83.
13. de Vega JM, Díaz J, Serrano E, Carbonell LF. Oxidative stress in critically ill patients with systemic inflammatory response syndrome. Critical care medicine. 2002 Aug 1;30(8):1782-6.
14. de Vega JM, Díaz J, Serrano E, Carbonell LF. Plasma redox status relates to severity in critically ill patients. Critical care medicine. 2000 Jun 1;28(6):1812-4.
15. Pascual C, Karzai W, Meier-Hellmann A, et al. Total plasma antioxidant capacity is not always decreased in sepsis. Critical Care Medicine. 1998 Apr 1;26(4):705-9.
16. MacKinnon KL, Molnar Z, Lowe D, Watson ID, Shearer E. Measures of total free radical activity in critically ill patients. Clinical biochemistry. 1999 Jun 1;32(4):263-8.
17. Meneshian A, Bulkley GB. The physiology of endothelial xanthine oxidase: from urate catabolism to reperfusion injury to inflammatory signal transduction. Microcirculation. 2002 Jun;9(3):161-75.
18. Terada LS, Guidot DM, Leff JA, et al. Hypoxia injures endothelial cells by increasing endogenous xanthine oxidase activity. Proceedings of the National Academy of Sciences. 1992 Apr15;89(8):3362-6.
19. Zoccali C, Maio R, Mallamaci F, Sesti G, Perticone F. Uric acid and endothelial dysfunction in essential hypertension. Journal of the American Society of Nephrology. 2006 May 1;17(5):1466-71.
20. Chonchol M, Shlipak MG, Katz R, et al. Relationship of uric acid with progression of kidney disease. American Journal of Kidney Diseases. 2007 Aug 1;50(2):239-47.
21. Suliman ME, Johnson RJ, García-López E, et al. J-shaped mortality relationship for uric acid in CKD. American Journal of Kidney Diseases. 2006 Nov 1;48(5):761-71.
22. Jabs CM, Sigurdsson GH, Neglen P. Plasma levels of high-energy compounds compared with severity of illness in critically ill patients in the intensive care unit. Surgery. 1998 Jul 1;124(1):65-72.
23. Chuang CC, Shiesh SC, Chi CH, et al. Serum total antioxidant capacity reflects severity of illness in patients with severe sepsis. Critical Care. 2006 Feb;10(1):R36.
24. Aljmor AA, Alazawi DS, Hasan AS. Assessment of Serum Uric Acid and Highly Sensitive C-reactive Protein in Patients with Acute Respiratory Distress Syndrome. Iraqi Journalof Community Medicine. 2019;32(1):7-12.
25. Nagaya N, Uematsu M, Satoh T, et al. Serum uric acid levels correlate with the severity and the mortality of primary pulmonary hypertension. American Journal of Respiratory and Critical Care Medicine. 1999 Aug 1;160(2):487-92.