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# Hyperuricaemia as a predictor of hospital outcome in patients with sepsis: results of a prospective study

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## Abstract

**Background:** Early management of sepsis in the emergency department improves patient outcomes. The identification of at-risk patients for aggressive management by an easily available biomarker could go a long way in the triage of patients in the emergency department. It is postulated that during sepsis, the majority of patients undergo ischaemic reperfusion injury or inflammation, and uric acid with its oxidant and antioxidant properties may be playing some role and, hence, the measurement of uric acid could possibly predict the hospital course in patients with sepsis. We were prompted to undertake this study as serum uric acid estimation is readily available and economical compared to newly evolving biomarkers in sepsis. Estimation of serum uric acid levels on arrival to the emergency department may prove a useful predictor of hospital outcome in patients with sepsis especially in regions with limited resources.

**Results:** Of 102 patients, 55 (53.9%) were males. The mean age of the study cohort was  $63.2 \pm 10.48$ . Patients with higher qSOFA scores had higher uric acid levels on admission. While 12 (11.8%) patients had a septic shock, acute kidney injury was recorded in 48 (47.1%) patients and 11 (10.8%) patients required dialysis. Thirty-four (33.3%) patients had respiratory failure, and of these, 21 (20.6%) patients required mechanical ventilation. The overall median stay in the medical intensive care (MICU) was 3 days (range 2–7 days). The patients with higher uric acid levels had higher rates of respiratory failure but did not reach significant levels. In 15 (14.7%) patients, 7 males expired (mortality rate of 14.7%). There was a significant association between SOFA score and mortality. Patients who succumbed to sepsis had higher serum uric acid levels on arrival.

**Conclusions:** Patients with higher qSOFA scores had higher uric acid levels on admission. Hyperuricaemia predicted acute kidney injury, a requirement of mechanical ventilation and mean hospital stay in patients with sepsis. Further studies may be required to confirm the association.

**Keywords:** Hyperuricaemia, Mechanical ventilation, qSOFA score, Sepsis, Dialysis

## Background

The dawn of recognition of sepsis began thousands of years back, when Hippocrates claimed that sepsis was the process by which flesh rots and wounds fester [1]. Since then, the quest to detect early sepsis continued, and the measure breakthrough towards this aim was when

microbes were held responsible for sepsis [2]. Sepsis is one of the major causes of mortality and morbidity all over the globe. Murphy et al. in their study concluded that septicemia was the 11th leading cause of death in the USA during 2010 [3]. Time is the key in the management of sepsis. Studies have shown that an early, aggressive treatment of sepsis in the emergency department significantly improves patient outcomes. In a retrospective analysis of more than 28,000 patients with severe sepsis in the hospital, mortality was shown to peak every hour and antibiotic administration was delayed [4], and

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another study had similar results [5]. Thus, emergency department triage becomes very crucial in preventing mortality and morbidity of septic patients. Of various attempts to triage at-risk patients in the emergency room, one of the attempts was to recognise clinically, at-risk patients, and the development of quick sequential organ failure assessment (qSOFA) score came into existence [6]. Even though this scoring system helped to predict fatal outcomes in sepsis syndrome in various emergency departments, its predictive value was found to be low and attempts to modify were done by adding age to the scoring system by Cag et al. [7]. The identification of at-risk patients for an aggressive management by an easily available biomarker could go a long way in the triage of patients in the emergency department. It is postulated that during sepsis, the majority of patients undergo ischaemic reperfusion injury or inflammation, and uric acid with its oxidant and antioxidant properties may be playing some role and, hence, the measurement of uric acid could possibly predict the hospital course in patients with sepsis [8]. While the quest for a perfect biomarker for an early detection of patients at risk for complications continues, serum uric acid has been studied as the potential biomarker by various workers in the recent past [8–10]. Uric acid, the end product of purine metabolism in humans, is produced either endogenously or as a result of nucleic acid break down. As most of it is excreted by the kidneys, the fractional excretion of uric acid is decreased in patients with hyperuricaemia. The rising uric acid levels in the body are harmful and have been implicated in kidney disease, hypertension and cardiovascular diseases [8]. We were prompted to undertake this study as serum uric acid estimation is readily available and economical compared to newly evolving biomarkers in sepsis. Estimation of serum uric acid levels on arrival to the emergency department may prove a useful predictor of hospital outcome in patients with sepsis especially in regions with limited resources.

## Methods

This prospective study was carried out at Government S.M.H.S Hospital, Srinagar, Kashmir, a tertiary care centre in the valley of Kashmir from July 2017 to June 2018. The patients with sepsis were enrolled, and their quick sequential organ failure assessment (qSOFA) score [6] was calculated at the time of admission. Septic screen and serum uric acid levels were measured in all patients. The study was conducted in full compliance with the Declaration of Helsinki and as per the research guidelines of the Government Medical College, Srinagar, Kashmir. An informed consent was taken from the patients or their attendants for the estimation of serum uric acid levels. The patients were triaged in the emergency room

depending upon the qSOFA score and were admitted in the ward or medical intensive care.

## Enrolment criteria

### Inclusion criteria

The inclusion criteria are patients' age > 18 years with any of the criteria of systemic inflammatory response temp > 38 °C, leucocytosis or leucopenia

### Exclusion criteria

Patients with sepsis having (1) diabetic ketoacidosis, (2) hypothyroidism and (3) haematological malignancies and chronic renal failure were excluded.

After an initial history and clinical examination based on a predefined approved pro forma, the demographic data of the study participants was completed. This included patients' age, gender and co morbid illness, and qSOFA score of each patient was calculated.

The blood samples were taken for complete blood count CBC, liver function tests, renal function tests and serum uric acid levels.

The patients were started on broad-spectrum antibiotics after fluid resuscitation when required. Depending upon oxygen saturation on room air, patients were given high-flow oxygen or put on mechanical ventilation when indicated. Patients with a qSOFA score > 2 were admitted in medical intensive care and were monitored for the requirement of mechanical ventilation or dialysis.

The final outcomes of the study were mean hospital stay, need for dialysis, mechanical ventilation and mortality in relation to serum uric acid levels.

## Definitions

1. Sepsis was defined based on the Society of Critical Care Medicine, Surviving Sepsis Campaign 2012 definition [11].
2. Hyperuricaemia: The serum uric acid level  $\geq$  7 mg/dL in both males and females was considered as hyperuricaemia.
3. Acute kidney injury: An increase in serum creatinine > 0.3gm/dl above 1 mg/dl over a period of 48 h.
4. qSOFA score: We calculated the quick sequential organ failure assessment (qSOFA) score [6].
5. Acute respiratory distress syndrome (ARDS) was defined as per the Berlin definition [12].

## Statistical analysis

The data was entered on Microsoft Excel and the percentages of measures by uric acid level were compared using the chi-squared tests for association. For qSOFA scores, linear regression was performed to assess the

linear association with uric acid. All analyses were performed in SAS 9.4.

## Results

Of the 102 patients, there were 55 (53.9%) males. The mean age of the study cohort was  $63.2 \pm 10.48$  years, and age ranged from 22 to 72 years. The patients with higher

SOFA scores had higher uric acid levels on admission. During the study period, 12 (11.8%) patients had septic shock who were managed in the medical intensive care of the hospital initially with broad-spectrum antibiotics and later as per the sensitivity pattern. The supportive care was given to all the patients in the study cohort as per the sepsis protocol guidelines. Acute kidney injury due to sepsis was recorded in 48 (47.1%) patients, and 11 (10.8%) patients required dialysis. Thirty-four (33.3%) patients had respiratory failure, and of these, 21 (20.6%) patients required mechanical ventilation. The overall median stay in medical intensive care was 3 days, and MICU stay ranged from 2 to 7 days. The details are shown in Table 1.

The patients with hyperuricaemia at presentation had significantly higher acute kidney injury rates during their hospital stay. They had significantly higher requirements for dialysis compared to those who had lower uric acid levels on admission. The details are shown in Table 2. The patients with higher uric acid levels had higher rates of respiratory failure but did not reach significant levels. The details are shown in Table 3

**Table 1** Demographic and clinical characteristics of patients

Characteristic	Frequency (percent)
Age in years (mean, SD)	63.2 $\pm$ 10.48
Males	55 (53.9%)
Shock	12 (11.8%)
AKI	48 (47.1%)
Dialysis	11 (10.8%)
Respiratory failure	34 (33.3%)
MICU stay in days (median, range)	3, 2 to 7
Intubation	21 (20.6%)
Death	15 (14.7%)

**Table 2** Demographic and clinical parameters according to the outcome

Characteristic	Died (n = 15)	Survived (n = 87)	Unadjusted OR (95% CI)	P value
Age in years (mean, SD)	68.3 (8.74)	62.3 (10.54)	1.064 (1.002–1.129)	0.038
Sex				
Male	7	48	0.711 (0.237–2.133)	0.542
Female	8	39	x	
MICU stay in days (median, range)	4, 3–5	2, 2–7	2.389 (1.468–3.890)	< 0.001
Shock				
Yes	7	5	14.350 (3.691–55.797)	< 0.001
No	8	82	x	
Dialysis				
Yes	6	5	10.933 (2.773–43.110)	< 0.001
No	9	82	x	
Respiratory failure				
Yes	12	22	11.818 (3.050–45.787)	< 0.001
No	3	65	x	
AKI				
Yes	14	34	21.824 (2.743–173.634)	< 0.001
No	1	53	x	
Intubation				
Yes	15	6	x	< 0.001
No	0	81	x	
Raised serum uric acid				
Yes	13	35	9.657 (2.051–45.461)	0.001
No	2	52	x	
QSOFA				
2	2	68	23.263 (4.824–112.174)	< 0.001
3	13	19	x	

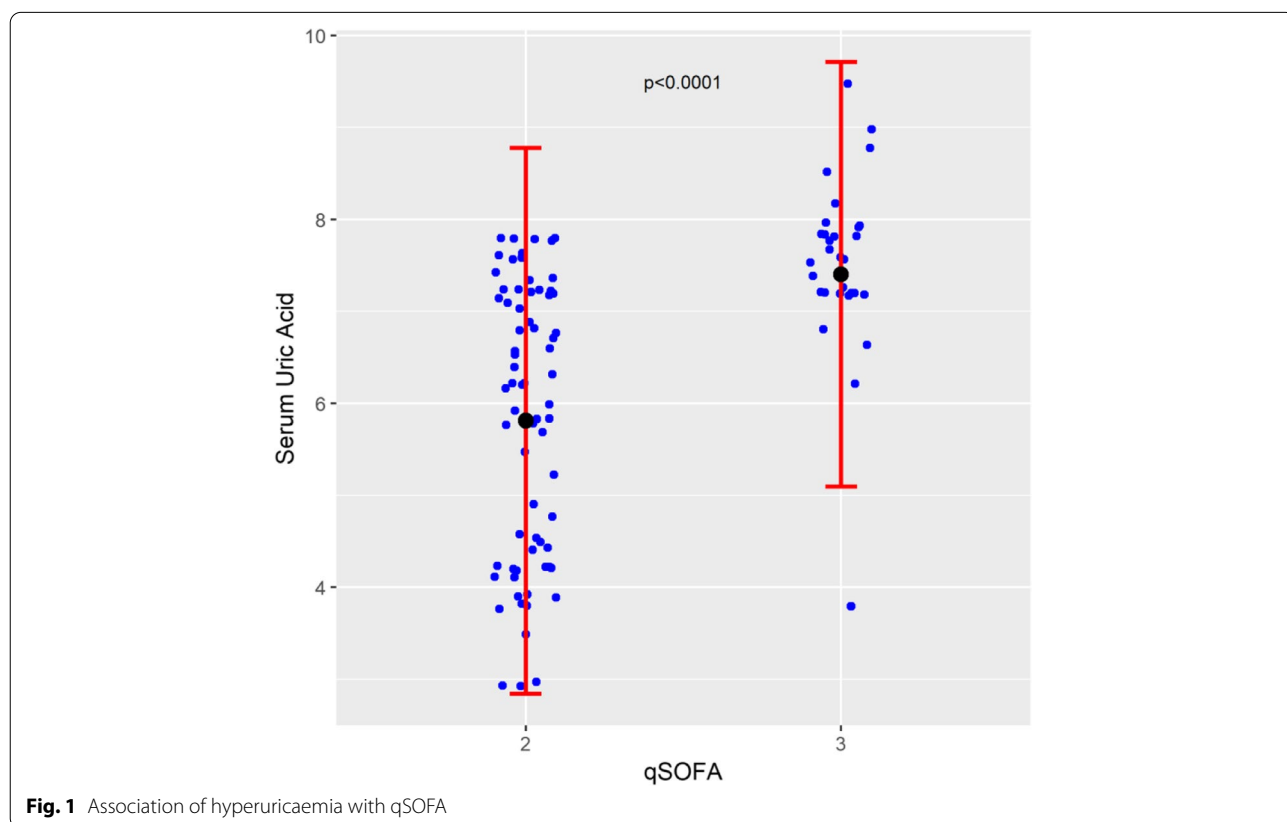
**Table 3** Multivariable regression analysis for the predictors of death

	Odds ratio	95% CI		P value
		Lower limit	Upper limit	
Raised uric acid	4.702	0.630	35.095	0.131
AKI	18.448	1.806	188.432	0.014
Respiratory failure	2.060	0.364	11.673	0.414
Age < 60	5.271	0.909	30.557	0.064
QSOFA	8.888	1.408	56.127	0.020

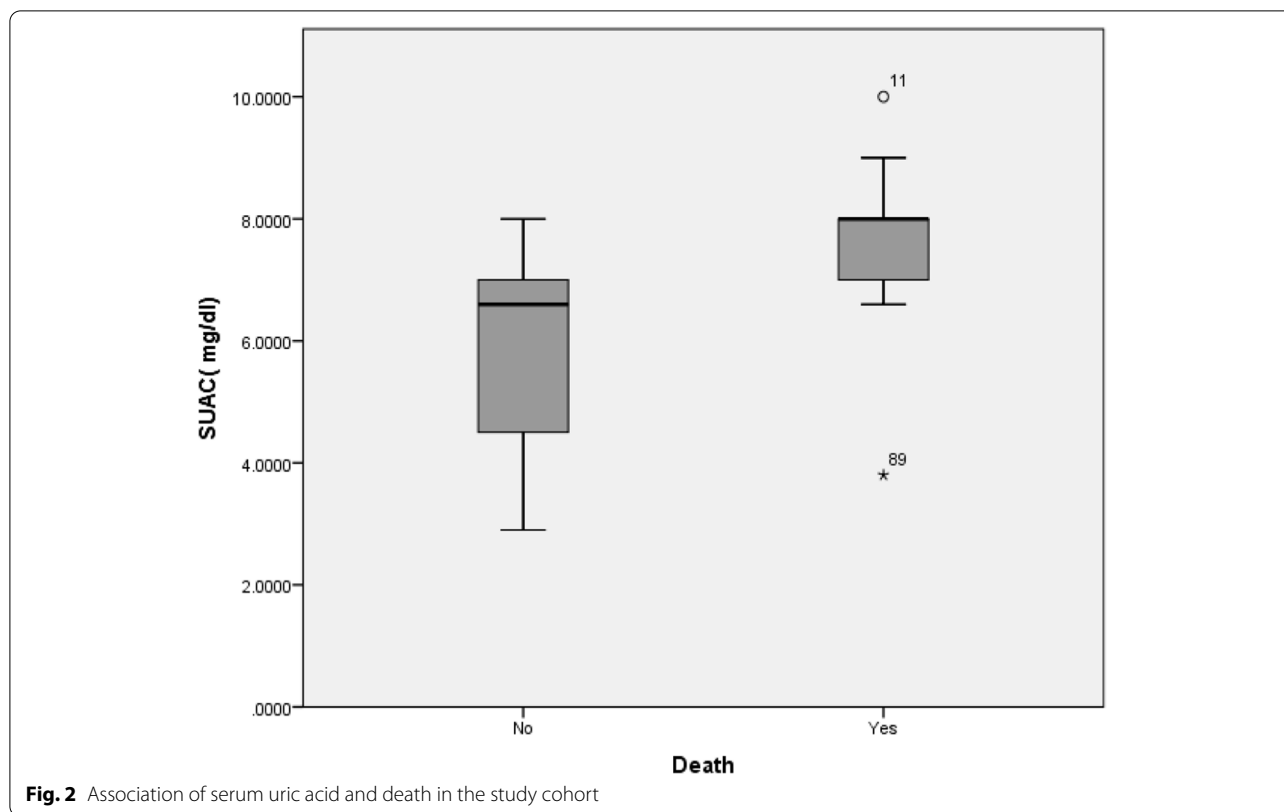
and Fig. 1 In this study, 15 (14.7%) patients expired in our study cohort (mortality rate of 14.7%). There were 7 males, and there was no significant association between mortality and gender. However, there was a significant association between SOFA score and mortality. There was a significant difference in age between the survived group and those who expired. The patient who expired had a higher stay in medical intensive care compared to those who survived ( $p$  value = < 0.001). The details are shown in Table 3. Patients who succumbed to sepsis had higher serum uric acid levels on arrival as shown in Fig. 2.

**Discussion**

The results of our study showed that patients with hyperuricaemia on arrival to the emergency room were at higher risk of acute kidney injury, and the overall prognosis including mortality rate was poor in patients with hyperuricaemia on arrival to the emergency department. Our results are in line with other researchers [8–10]. Our study revealed a significant difference between hospital stay need for mechanical support and mortality between the two groups (hyperuricemic and normouricemic group) as shown in Table 3. Elevated serum uric acid levels are known to activate various inflammatory mediators, cause endothelial dysfunction and subsequently affect the course in a given case of sepsis. In a study by Akbar et al., the data on 144 patients admitted in medical intensive care hyperuricaemia on admission in patients with sepsis was found to be associated with poor prognosis, and patients with high uric acid levels had an increased medical intensive care stay. The authors in the above-mentioned study concluded that patients with hyperuricaemia were more prone to an increased risk for acute kidney injury and ARDS [8]. Our results are in cognisance to their results as patients with hyperuricaemia on arrival had significantly prolonged stay in the medical intensive care. In another large study, hyperuricaemia



**Fig. 1** Association of hyperuricaemia with qSOFA



was associated with a higher risk for in-hospital acute kidney injury (AKI) [13]. Various mechanisms attributed to hyperuricaemia-induced AKI include crystal precipitation in addition to various non-crystal mechanisms due to hyperuricaemia leading to AKI as described by Kaushik et al. [14]. Acute kidney injury subsequently leads to a cascade of complications and finally affecting the outcome in a given case of sepsis. Vieira et al. in their study demonstrated that renal dysfunction negatively affected the course of the patient which could range from duration of mechanical ventilation to mortality in patients with sepsis [15]. Thus, estimation of uric acid levels on arrival to the emergency department could predict the course of sepsis. In our study, 48 (47.1%) patients had acute kidney injury and 11 (10.8%) patients required dialysis as shown in Table 1. It may be prudent to mention that time is very crucial in the management of sepsis as an acute kidney injury invariably develops within 24 h after admission to ICU, and septic AKI is independently associated with poor prognosis [3].

Hyperuricaemia has also been shown to correlate not only with the incidence of pulmonary diseases but also determines the severity and outcome of pulmonary diseases. The data on 237 patients from Korea revealed that patients with low serum uric acid had significantly better survival rate compared to those with

hyperuricaemia, and the authors believed that serum uric acid could be utilised as a prognostic marker in patients with ARDS [16]. There is a synergistic relation between AKI and ARDS as ARDS has been shown to be a risk factor for AKI in critically ill patients [17]. The importance of hyperuricaemia was further highlighted in a study by Rodenbach et al. The authors in the above-mentioned study observed that hyperuricaemia in children and adolescents is a risk factor for the progression of CKD. The authors in the same study suggested uric acid-lowering therapy as a measure of retarding CKD progression in children [18].

The production of pro-inflammatory cytokines like tumour necrosis factor- $\alpha$  (TNF) and interleukin-1 is considered to be the hallmarks in the pathophysiology of sepsis. In an animal model, it was observed that high uric acid levels lead to a surge in TNF production, and the authors postulated that hyperuricaemia probably plays an important role in this phenomenon [19]. In another study, it was observed that patients with detectable TNF are susceptible to have more often and severe adult respiratory distress syndrome [20]. Plasma antioxidant potential is reduced early in the course of sepsis but finally it steeply during sepsis, and it is believed that failure in the reduction of plasma antioxidant potential is associated with an unfavourable outcome [21].

In another study, hyperuricaemia in the emergency department predicted the requirement of mechanical ventilation in a patient with sepsis [22]. The results of our study are in line with this study as 34 (33.3%) patients had respiratory failure, and of these, 21 (20.6%) patients required mechanical ventilation. The patients with higher uric acid levels had higher rates of respiratory failure but did not reach significant levels as shown in Table 2.

The limitation of the study we believe is that there was a lesser number of patients in the study; nevertheless, we believe that measurement of serum uric acid levels at the arrival of the patient predicts the severity of the illness in a given patient with sepsis.

## Conclusions

From the discussed results, it may be concluded that serum uric acid on arrival predicts hospital stay, need for dialysis and mechanical ventilation in patients with sepsis. The mortality rates in hyperuricaemia patients are higher compared to those with low uric acid levels on arrival to the emergency room. Further studies may be required to confirm the association.

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## Authors' contributions

BA: principal investigator, data collection, think tank and idea assessment. MN: data assimilation, statistical analysis, paper writing, corresponding author and idea assessment. MW: statistical analysis, data assimilation, think tank and idea assessment. RR: data collection, think tank and idea assessment. TA: data collection, think tank and idea assessment and paper writing. The author(s) read and approved the final manuscript.

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## Availability of data and materials

The whole data is available in crude paper as well as soft copy format.

## Declarations

### Ethics approval and consent to participate

The study was conducted in full compliance with the Declaration of Helsinki and as per the research guidelines of the Government Medical College, Srinagar, Kashmir, under serial number 2017/PGRP/gmcethcommitte dated July 2017.

### Consent for publication

An informed consent was taken from the patients or their attendants for the estimation of serum uric acid levels.

An informed consent was taken from patients and attendants for the research publication of the data for educational purposes.

Consent has been taken from all the authors in person.

### Competing interests

The authors declare that they have no competing interests.

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