



Research Article

RELATIONSHIP OF SERUM URIC ACID WITH SEVERITY OF SCRUB TYPHUS

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ABSTRACT

**Background:** Scrub typhus is a major public health problem in Asia Pacific region and is endemic in many countries including India. Million of cases have been reported annually during monsoon and post monsoon period. This study aims to find a serum biomarker to predict the severity of disease.

**Methods :** Authors conducted a hospital based study in Department of Medicine in sub Himalayan regions in patients of scrub typhus from June 2017-2018.

**Results:** Forty seven (53.4%) out of 88 patients of severe scrub typhus had hyperuricemia ( $p < 0.05$ ). The patients with hyperuricemia had significant transaminitis ( $p < 0.001$ ), raised serum creatinine ( $p = 0.008$ ), thrombocytopenia ( $p = 0.001$ ) and among the patients who died 40% had hyperuricemia. Thus serum uric acid levels had significant correlation with the severity of the disease.

**Conclusion:** The patients of scrub typhus with raised serum uric acid levels are associated with increased disease severity and morbidity.

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INTRODUCTION

Scrub typhus, also known as tsutsugamushi disease [Japanese word tsutsuga (“dangerous”), mushi (“bug”) ] is an acute febrile illness caused by *Orientia tsutsugamushi*, a small Gram negative obligate intracellular organism.<sup>1</sup>

The rickettsiae multiply in the endothelium of the blood vessels leading to cellular infiltration of the vessel walls, perivascular accumulation of mononuclear cells and occasionally thrombosis and haemorrhage and finally all the evident pathological changes.<sup>2</sup>

Mortality can occur from either primary infection or complications like pneumonitis, ARDS, encephalitis, circulatory failure. Scrub typhus is one of the most common cause of sepsis and septic shock in endemic areas.<sup>3</sup>

The pathogenesis of increased uric acid in sepsis is not known exactly and could be due to increased production as well as decreased excretion of uric acid. Hypoxia and ischemia occurring in sepsis leads to activation of endothelial xanthine oxidase that converts xanthine and hypoxanthine into uric acid.<sup>4</sup> Increased uric acid in serum leads to decreased release of vasorelaxation factors from the endothelium that leads to ischemia and finally leads to dysfunction of the internal organs.<sup>5</sup> Thus serum uric acid levels can be used as a sole marker of severity of illness in sepsis.<sup>6</sup>

METHODS

**Study design:** Cross sectional (longitudinal).

**Study area:** Medicine intensive care unit / ward of IGMC Shimla during a period of 1 year (June 2017-June 2018)

**Inclusion Criteria:** Patients age >18yrs diagnosed with Scrub typhus by IgM antibodies by ELISA method.

**Exclusion Criteria:**

1. Conditions altering serum uric acid levels including chronic kidney disease, liver disease, gout, alcoholism, violent exercise, hematological malignancy, patients on chemotherapy for malignancies.
2. History of intake of drugs that may alter serum uric acid levels, like loop diuretics, thiazide diuretics, indapamide, metolazone, salicylates, ethambutol, amiloride, cisplatin, cyclosporine, cyclophosphamide, ethacrynic acid, ketoconazole, levodopa, pentamidine, phencyclidine, pyrazinamide, theophylline, vitamin C.
3. Patients not willing to participate in study.

Operational Definitions

Severe disease

A case of scrub typhus fulfilling the criterion of severe sepsis or septic shock or evidence of organ system failure are defined as severe disease.

Sepsis<sup>7</sup>

Defined as at least two of the following signs and symptoms (SIRS) that are both present in suspicion of new infection.

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- Hyperthermia >38.3°C or Hypothermia <36°C
- Tachycardia >90 bpm
- Leukocytosis (>12,000  $\mu\text{L}^{-1}$ ) or Leukopenia (<4,000  $\mu\text{L}^{-1}$ ) or >10% bands
- Tachypnea >20/min

**Severe sepsis<sup>7</sup>**

Severe sepsis includes SIRS and at least one of the following signs of hypo perfusion or organ dysfunction that is new and not explained by other known aetiology of organ hypofunction

1. **Cardiovascular:** Arterial systolic blood pressure  $\leq 90$  mm Hg or mean arterial pressure  $\leq 70$  mm Hg that responds to administration of IV fluid.
2. **Renal:** Urine output <0.5 ml/kg per hour for 1 h despite adequate fluid resuscitation.
3. **Respiratory:**  $\text{Pao}_2/\text{Fio}_2 \leq 250$  or if lung is the only dysfunctional organ,  $\leq 200$ .
4. **Hematologic:** Platelet count <80, 000/ $\mu\text{l}$  or 50% decrease in platelet count from highest value recorded over previous 3 days.
5. **Unexplained metabolic acidosis:** A pH  $\leq 7.30$  or a base deficit  $\geq 5.0$  mEq/L and plasma lactate level > 1.5 times upper limit of normal for reporting lab.

**Septic shock<sup>7</sup>**

Sepsis with hypotension (arterial blood pressure <90 mm Hg systolic or 40 mm Hg less than patient's normal blood pressure) for at least 1 h despite adequate fluid resuscitation or need for vasopressors to maintain systolic blood pressure  $\geq 90$  mm Hg or mean arterial pressure  $\geq 70$  mm Hg.

**Organ system failure<sup>8</sup>**

**Neurologic:** Glasgow Coma Score < 6 (in absence of sedation)

**Cardiovascular:** Heart rate < 54 beats per min or Mean arterial blood pressure < 49 mm Hg (systolic blood pressure < 60 mm Hg) or ventricular tachycardia/ ventricular fibrillation or both or Serum pH < 7.24 with a  $\text{PaCO}_2$  of < 49mm Hg.

**Pulmonary:**  $\text{PaCO}_2 > 50$  mm Hg (acutely) or (A-a)DO<sub>2</sub> > 350 mm (Hg (A- a)DO<sub>2</sub> = [713 x FiO<sub>2</sub> - ( $\text{PaCO}_2/\text{RQ})$  - PaO<sub>2</sub>] or Ventilator or continuous positive airway pressure dependence on the second day of organ dysfunction

**Hepatic:** Jaundice (bilirubin > 6 mg/100 dL) or Coagulopathy (prothrombin time 4 sec greater than control, in the absence of anticoagulation)

**Renal:** Urine output < 479 mL/24 hr or < 159 mL/8 hr or Serum BUN > 100 mg/100 dL or Serum creatinine > 3.5 mg/100 dL

**Hematologic:** White blood count < 1, 000 cells/  $\text{mm}^3$  or Platelets < 20, 000 or Hematocrit < 20%.

**Serum Uric Acid:** Normal range as per our laboratory being 2.4-5.7 mg/dl in females and 3.4-7.0 mg/dl in males;done by enzymatic, calorimetric technique using auto analyzer.<sup>9</sup>

**RESULTS**

Total 203 patients of scrub typhus were included in the study. The clinical and laboratory profile and course in hospital were documented. Fever was present in all patients. Chills and rigors in 115 (56.65%), headache in 59 (29.06%), vomiting in 41(20.20%), altered sensorium 26 (12.81%), diarrhoea in 21

(10.34%), abdominal pain in 40(19.70%), myalgia in 18(8.72%) patients were noted.(Table 1)

**Table 1** Clinical Features at presentation (n =203)

S. No	Chief Complaints	Frequency (n)	Percent age (%)
1.	Fever	203	100
2.	Chills and rigors	115	56.65
3.	Headache	59	29.06
4.	Cough	56	27.59
5.	Vomiting	41	20.20
6.	Abdominal pain	40	19.70
7.	Altered sensorium	26	12.81
8.	Loose stools	21	10.34
9.	Myalgia	18	8.72
10.	Seizure	2	0.99

On examination 131 (66.01%) had tachycardia, 21(10.34%) had hypotension, 53 (26.11%) patients had eschar .(Table 2)

**Table 2** Clinical Signs among the study population (n=203)

S. No	Finding	Frequency (n)	Percentage (%)
1.	Tachycardia	131	66.01
2.	Icterus	57	28.08
3.	Eschar	53	26.11
4.	Temp >102	32	15.7
5.	Hypotension	21	10.34

Leucocytosis in 51 (25.12%), leucopenia in 6(2.95%) and thrombocytopenia in 171(84.23%) were main haematological abnormalities. Hyperbilirubinemia in 64 (31.52%), transaminitis in 95 (46.79%), raised alkaline phosphatase in 121 (59.61%) and hypoalbuminemia in 172 (84.72%) patients were the other main laboratory abnormalities noticed. Raised serum creatinine was observed in 67(33.01%) of patients and raised BUN was noted in 55 (27.09%) patients. (Table 3)

**Table 3** Lab abnormalities in the study group (n=203)

S.No	Parameter	Frequency(n)	Percentage (%)
1	Leukocytosis (>12000)	51	25.12%
2	Leukocytopenia(<4000)	6	2.95%
3	Thrombocytopenia(<1.5laks)	171	84.23%
4	Hyperbilirubinemia(>2mg/dl)	64	31.52%
5	Transaminitis (OT/PT>100)	129	63.54%
6	Hypoalbuminemia(<3.5 g/dl)	172	84.72%
7	S. creatinine (>1.5 mg/dl)	67	33.01%
8	S. urea (>40mg/dl)	109	53.69%

**Relationship of Serum Uric acid with Scrub Typhus**

88 (43.3%) out of 203 patients had severe scrub typhus and 45 (51.1%) of them had hyperuricemia and remaining 43(48.9 %) patients with severe disease had normal serum uric acid levels.

Out of total 203 patients in study group, 61(30%) patients had hyperuricemia and 45 (73.7%) of them had severe scrub typhus.(Figure no 1)

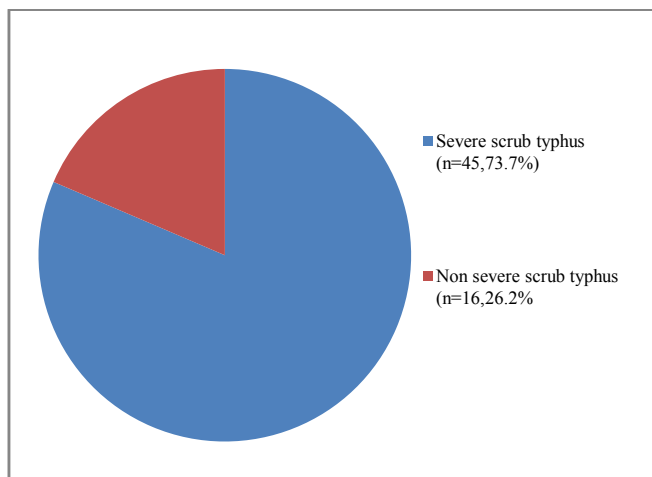


Figure 1 Patients of scrub typhus with hyperuricemia(n=61)

Total 21 (10.3%) out of 203 patients had hypotension and 11 (52.3%) of them had hyperuricemia. Among the 88 patients with severe scrub typhus 18 (20.4%) patients had hypotension and 9 (50%) among them had hyperuricemia .

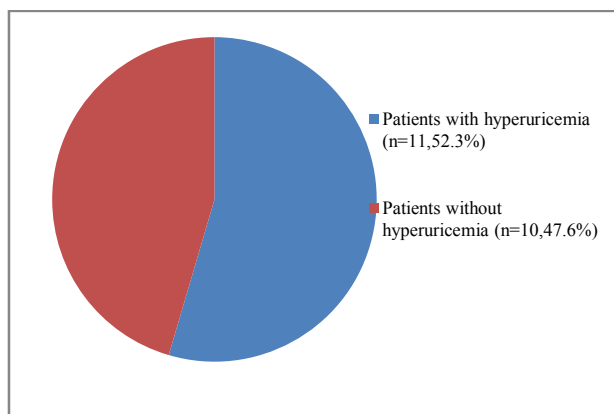


Figure 2 Patients of scrub typhus with hypotension (n=21)

Among the laboratory parameters 61 (30.0%) patients of scrub typhus with hyperuricemia showed higher mean serum bilirubin and transaminitis (serum bilirubin, SGOT and SGPT;  $p < 0.05$ ) . 55 patients had BUN  $> 100$  mg/dl, 35 (63.5 %) of these 55 patients had hyperuricemia. 26 patients had serum creatinine  $> 3.5$  mg/dl and 18 (69.2%) of these 26 patients had hyperuricemia.

Table 4 Comparison of Biochemical parameters in relation to Serum Uric acid

S.No	Parameter	With Hyperuricemia		Without hyperuricemia		p value
		Mean	SD	Mean	SD	
1	Bilirubin (mg/dl)	2.56	3.03	1.99	2.38	0.021*
2	SGOT(IU/L)	281	447.8	200	204	<0.001*
3	SGPT(IU/L)	202	313.96	143	146	<0.001*
4	ALP(IU/L)	259	257.18	243	240	0.508
5	Protein (g/dl)	5.7	0.988	5.79	1.07	0.4530
6	Serum Albumin(g/dl)	2.8	0.711	2.88	0.704	0.9045
7	Urea(mg/dl)	102	57.93	53.54	49.18	0.117
8	Creatinine(mg/dl)	3.0	1.902	1.24	1.44	0.008*

\*p value <0.05 is considered as significant.

In our study, thrombocytopenia and renal functions were deranged in patients of scrub typhus with hyperuricemia than those without hyperuricemia. ( $p < 0.001$ ). (Table 5).

Table 5 Distribution of patients according to disease severity

S.No	Severity Criterion	All Patients (203)	With Hyperuricemia (61)	Without Hyperuricemia (142)	p value
1	Severe sepsis	88	47	41	<0.001
2	Septic shock Organ failure	18	9	9	0.068
3	BUN >100 (mg/dl)	55	35	20	<0.001
4	Creatinine >3.5(mg/dl)	26	18	8	<0.001
5	Bilirubin >6(mg/dl)	18	10	8	0.01342
6	Platelets <20000 (lacs/dl)	22	13	9	0.00165

Out of total 61 patients of scrub typhus with hyperuricemia, 47 (77.04%) patients had severe scrub typhus and remaining 14 patients did not fulfil the criteria of severe scrub typhus as per our study definition. These patients with hyperuricemia constitute 53.40% of total patients with severe scrub typhus and was statistically significant ( $p = < 0.05$ ).

Table 6 Relation between Hyperuricemia and Severity of Scrub Typhus (n=88)

Hyperuricemia	Severity (n)	Severity (%)	p value
Present	47	53.40	<0.05
Absent	41	46.59	

Chi square =42.45, DF = 1

## DISCUSSION

No studies are available regarding association of serum uric acid levels with disease severity in patients of scrub typhus. Thus we compared findings of our study with studies showing association of serum uric acid levels in sepsis caused due to non scrub typhus disease.

A study done in 2014 in West Virginia between January 2014 to July 2014 among 144 patients admitted to the Medical Intensive Care Unit (MICU) at Ruby Memorial Hospital, hypothesized that elevated uric acid in patients with sepsis increases the morbidity. The primary end point was the correlation between hyperuricemia and the morbidity rate. 54 patients (37.5%) had hyperuricemia. Severity of illness can be assessed by the duration of stay in ICU. Study found that overall 75% and 54.2% of patients were still in the ICU at 48 and 72 hours, respectively. The probability of having a uric acid level less than 7 mg/dl with ICU stay at 48 and 72 hours was 71.1% and 47.8% respectively. However the probability of ICU stay in patients with hyperuricemia at 48 and 72 hours was 81.5% and 64.8% respectively. These probabilities have a p value of 0.0464 and 0.1209 respectively. Thus it was concluded that serum uric acid levels can be potentially used as a sole marker of severity of illness and predictor of morbidity in sepsis.<sup>6</sup>

A study done in Iran on 120 critically ill patients to evaluate the validity of serum uric acid in prediction of mortality. They divided the patients into two groups, one with uric acid levels more than 7.3 mg/dl and other with uric acid levels less than 7.3 mg/dl. Patients with average serum uric acid level  $7.82 \pm 2.82$  required mechanical ventilation and those with average uric acid levels  $6.16 \pm 2.7$  didnot require mechanical ventilation. This result was statistically significant.<sup>10</sup> Our study also found that the patients requiring mechanical ventilation, the average serum uric acid level(  $8.72 \pm 2.1$  mg/dl)

was higher than those who did not require mechanical ventilation.

471 patients were studied by Zhu *et al* in Fudan University, Shanghai, China from January 2003 to April 2010. This study analyzed uric acid, serum creatinine, blood urea nitrogen (BUN) within 24 hours of admission. The patients who did not survive had a higher level of serum uric acid than the survivors.<sup>11</sup> Similarity with our study includes the significantly deranged renal parameters in patients with hyperuricemia and difference comprises that in our study it showed correlation with morbidity /organ failures and is related to prognosis of infection.

A study was done by Peralta Prado *et al* to know relation of uric acid and severity of sepsis. They excluded the patients with gout, on diet rich in amino acids or hyperproteic diet. The study included 38 patients aged 19-85 years (n=50) suffering from soft tissue infections and pneumonia. They found that patient with hyperuricemia had high APACHE II score. Study showed that the uric acid is an accessible and unexpensive marker to assess the severity and mortality of sepsis.<sup>12</sup> In our study we did not calculate APACHE score but the final results in both studies are similar in relation to serum uric acid and severity of infection.

#### Limitations

This study was conducted in a single centre on a small sample size. Though we tried to eliminate factors causing hyperuricemia in study population but baseline values of serum uric acid were not available.

#### CONCLUSION

Patients with severe scrub typhus have statistically significant thrombocytopenia, deranged renal and liver function. Severe sepsis, renal dysfunction and severe thrombocytopenia all are manifestations of severe disease and are indicative of underlying DIC. In this study severe sepsis, renal dysfunction and severe thrombocytopenia were significantly associated with patients of scrub typhus with hyperuricemia when compared with patients of scrub typhus without hyperuricemia indicating that the presence of hyperuricemia in patients of scrub typhus was associated with the severe disease. The patients of scrub typhus with raised serum uric acid levels are associated with increased disease severity and morbidity.

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**Conflict of interest:** None declared.

**Ethical approval:** The study was approved by the institutional ethics committee.

#### References

1. Hornick RB, Bennett JC, Plum F; Rickettsial disease; Goldman Cecil Textbook of Medicine. 21st ed. Philadelphia, USA: WB Saunders Company; 2000:1911-2.
2. Wang CC, Liu SF, Liu JW, Chung YH, Su MC, Lin MC. Acute Respiratory Distress Syndrome in scrub typhus. *Am J Trop Med Hyg*, 2007;76:1148-52
3. Thap LC, Supanaranond W, Treeprasertsuk S, Kitvatanachai S, Chinprasatsak S, Phonrat B. Septic shock secondary to scrub typhus: characteristics and complications. *The Southeast Asian Journal of Tropical Medicine and Public Health* Dec 2002; 33: 4.
4. A. Meneshian and G. B. Bulkley, The physiology of endothelial xanthine oxidase: from urate catabolism to reperfusion injury to inflammatory signal transduction. *Microcirculation* 2002; 9(3): 161-75.
5. Terada LS, Guidot DM, Leff JA, Willingham IR, Hanley ME, Piermattei D *et al* Hypoxia injures endothelial cells by increasing endogenous xanthine oxidase activity. *Proceedings of the National Academy of Science of the United States of America*: 1992 15;89(8):3362-63.
6. Akbar SR, Long DM, Hussain K, Alhajhusain A, Ahmed US, Iqbal HI *et al*. Hyperuricemia: An Early Marker for Severity of Illness in Sepsis *International Journal of Nephrology* 2015;2015 :301021.
7. Munford R. Severe Sepsis and Septic Shock. In Harrison's Principles of Internal Medicine. Kasper DL, Fauci AS, Hauser SL *et al* (Edi). 19<sup>th</sup> Edi. United States of America: McGraw Hill Education; 2015. 2; 1751.
8. Murray M, Coursin D. Multiple organ dysfunction syndrome. *Yale Journal of Biology and Medicine*. 1993; 66(5): 501-10.
9. Uric Acid plus 2016 *Rosch Diagnostics*.
10. Sun IO, Kim MC, Park JW, Yang MA, Lee CB, Yoon HJ, Kim JG, Lee KY: Clinical characteristics of acute kidney injury in patients with scrub typhus-RIFLE criteria validation. In: Proceedings of the 33<sup>rd</sup> Annual spring meeting meeting of the society of nephrology, 98, 2013.
11. Zhu HC and Cao RL. The relationship between serum levels of uric acid and prognosis of infection in critically ill patients *World J Emerg Med*. 2012; 3(3): 186-90.
12. Peralta-Prado AB, Ramírez-Hinojosa JP, Ramírez-Polo AI, López-Aguilar CE, Maya-Romero H, Carrillo-Espinoza R. Correlation of delta uric acid and the severity of sepsis *journal Medicina Interna de Mex* 2013; 29 (2).

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