

Procalcitonin Levels for Prognosis of Scrub Typhus Patients: A Retrospective Observational Analysis from a Tertiary Care Centre in Northern India

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ABSTRACT

Introduction: Scrub typhus is a major cause of acute febrile illness in India. It presents with various clinical features that vary from fever to multiorgan dysfunction. Similar symptoms and presentations cause difficulty in diagnosis. Therefore, it is important to have early and prompt diagnosis with better prognostic markers to decrease morbidity and mortality.

Aim: To determine the prognosis of scrub typhus patients based on the Procalcitonin (PCT) levels.

Materials and Methods: This retrospective observational study was conducted in the Microbiology Department of Sanjay Gandhi Postgraduate Institute of Medical Sciences, Uttar Pradesh, India, from January 2022 to January 2023. A total of 120 patients admitted to the hospital, who tested positive for Scrub typhus IgM by ELISA during this period and had a negative blood culture, were included in this study. Data analysis was conducted from February 2023 to April 2023. PCT levels of all these patients at the time of admission were recorded. The demographic information, laboratory parameters,

and treatment regimen of these patients were also compiled. Statistical analysis was performed, and p-value was used to determine statistical significance.

Results: The majority of the patients belonged to the age group of 21-40 years. Among these, elevated PCT values (ranging from 0.05-89.4 ng/mL) were observed in 112 (93.33%) patients. Twelve (10%) patients died during the study period, and all of them had elevated PCT levels. Among these, six developed septic shock with Multiple Organ Dysfunction Syndrome (MODS). Increased leukocyte values, elevated liver enzymes such as Aspartate Aminotransferase (SGOT/AST) and Alanine Transferase (SGPT/ALT), abnormal coagulation profile, and abnormal renal profile with elevated urea and uric acid levels were found to be significantly associated with scrub typhus patients with elevated PCT values.

Conclusion: There is a need to address the role of prognostic markers in the management of scrub typhus patients. This may lead to breakthroughs in the field of diagnostic research and help improve the prognosis of these patients.

INTRODUCTION

Scrub typhus, caused by *Orientia tsutsugamushi*, is a rickettsial disease endemic to the part of the world known as the "tsutsugamushi triangle" [1,2]. With an incubation period of 9-12 days, scrub typhus contributes to the major burden of acute undifferentiated febrile illness in India. Approximately one million cases of scrub typhus are reported in the Southeast Asian region every year [3,4]. Scrub typhus, which has a higher fatality rate, has recently spread throughout India and is a prominent cause of severe febrile illness. India's southern states, such as Tamil Nadu, Andhra Pradesh, Karnataka, and Kerala, its northern states of Himachal Pradesh, Uttarakhand, Jammu, and Kashmir, its northeastern states of Meghalaya, Assam, and Nagaland, its eastern states of West Bengal and Bihar, and its western states of Maharashtra and Rajasthan, have all reported high numbers of cases of this disease [3]. Due to common symptoms and presentation patterns in the Indian population, the disease is very difficult to clinically distinguish from other acute febrile diseases [5]. The disease presents with variable signs and symptoms such as fever, malaise, eschar, bleeding manifestations, and multi-organ dysfunction [6-8]. However, a delay in diagnosis and treatment may lead to major life-threatening complications such as Disseminated Intravascular Coagulation (DIC), meningoencephalitis, respiratory distress, and multi-organ failure [6,9].

The available diagnostics, such as Enzyme-linked Immunosorbent Assay (ELISA) and Immunofluorescence Assay (IFA), form the

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mainstay of scrub typhus diagnosis due to their high specificity and sensitivity. However, the detection of the early acute phase relies only on Polymerase Chain Reaction (PCR)-based methods. However, the applicability of PCR stands controversial due to the variegated genetic makeup of *Orientia tsutsugamushi* among its serotypes [10]. Additionally, there is a paucity of data on prognostic markers for scrub typhus.

Therefore, there is a necessity to address the role of prognostic markers in the management of scrub typhus patients to combat the worsening of their health. Whether Procalcitonin (PCT), a biomarker of bacterial sepsis, has any prognostic value in scrub typhus patients remains unexplored, and to date, there is a paucity of data regarding the significance of PCT in scrub typhus patients. The aim of this study was to determine the prognosis of scrub typhus patients based on the Procalcitonin (PCT) levels. Additionally, this study emphasises the role of vital laboratory parameters in the associated case fatalities in scrub typhus-positive patients.

MATERIALS AND METHODS

This retrospective observational study was conducted in the Microbiology department of Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India. All the data were collected from past records between January 2022 and January 2023, and data analysis was performed from February 2023 to April 2023.

The study was approved by the Institutional Ethics Committee (IEC code: 2021-109-IMP-EXP-38). As a time-bound study, only the records available during the study duration were considered. A total of 120 patients with scrub typhus who tested positive for Scrub typhus IgM by ELISA (InBios International Inc., Seattle WA, USA) were included in the study.

Inclusion criteria: The study included all patients with positive Scrub typhus IgM ELISA and a negative blood culture.

Exclusion criteria: Patients excluded from the study were those with concurrent dengue, malaria, leptospirosis, enteric fever, and viral hepatitis, as well as those with a known pre-existing liver or kidney disease, and those with any other detectable infective aetiology that could affect the PCT values.

Study Procedure

Patients meeting the inclusion and exclusion criteria underwent scrub typhus IgM ELISA on their blood samples. The procedure and interpretation of the ELISA followed the manufacturer's protocol. An optical density of ≥ 0.5 was considered diagnostic for scrub typhus [11]. PCT levels of all these patients at admission were recorded. PCT was measured using an assay with an analytic range of 0.05 to 200 μg per liter (VIDAS B.R.A.H.M.S PCT, bioMérieux). The guideline used the same cut-off values that were previously approved and utilised [12,13]. Basic demographic information, various laboratory parameters such as liver function tests, kidney function tests, coagulation profile, and treatment regimens of these patients were extracted from the Hospital Information System and compiled on an Excel sheet.

STATISTICAL ANALYSIS

Statistical tests were performed using Statistical Package for the Social Sciences (IBM-SPSS) software (Version 20; Armonk, NY) for descriptive statistics. The significance among percentages was calculated with the Chi-square test, and a p-value of < 0.05 was considered statistically significant. The numerical values were presented as mean and standard deviation.

RESULTS

During the study period, 120 patients who tested positive for scrub typhus IgM were included in the study. Among these, the majority of patients belonged to the age group of 21-40 years, followed by 41-60 years. The age range of the population was 3-80 years (Mean=38.3 years). The male-to-female ratio was 1.2:1. The laboratory parameters, including haemoglobin, total leukocyte count, platelet count, hepatic profile, and renal profile of the study population (n=120), are provided in [Table/Fig-1].

The treatment given to the patients during hospital stay is presented in [Table/Fig-2].

In all the patients included in the study, oral doxycycline (100 mg twice daily) was administered regardless of other clinical features. In cases of multi-organ dysfunction suggestive of scrub typhus, Faropenem or Amoxicillin-clavulanic acid were also administered along with doxycycline. Among the study population of 120 patients, elevated PCT values (0.05-89.4 ng/mL) were observed in 112 patients (93.33%) [Table/Fig-3].

The laboratory parameters were compared among the 120 patients with scrub typhus. Among these 120 patients, 17 patients had PCT values > 10 , which is considered elevated; the PCT ranged from 23.3 to 89.4 ng/mL. 12 (10%) died during hospitalisation with elevated PCT levels (26.5-89.4 ng/mL). Six of the deaths were caused by the development of septic shock with multiorgan involvement. Increased leukocyte values, elevated liver enzymes like SGOT and SGPT, elevated coagulation profile, and abnormal renal profile with elevated urea and uric acid levels were found to be significantly associated with mortality in scrub typhus patients with elevated PCT values [Table/Fig-4].

Parameters	Range	Mean \pm SD
Days of hospitalisation	2-50 days	19.83 \pm 8.21
Haemoglobin (g/dL)	2.1-16.2	10.36 \pm 2.55
Total Leucocyte count (cells/ μL)	3.7-31.8	11.25 \pm 5.63
Platelet count (platelets/ μL)	33-663	200.5 \pm 120.9
Alkaline phosphatase levels (U/L)	31-1465	301.5 \pm 260.1
SGOT/AST levels (U/L)	15-2217	150.6 \pm 292.2
SGPT/ALT levels (U/L)	11-1489	107.7 \pm 156.8
Amylase levels (U/L)	17-388	78.4 \pm 60.02
Conjugated bilirubin levels (mg/dL)	0.04-10.9	1.30 \pm 2.33
Total bilirubin levels (mg/dL)	0.19-17.2	2.07 \pm 2.87
Albumin levels (g/dL)	1.5-7.1	3.95 \pm 1.12
Urea levels (mg/dL)	10-301	58.79 \pm 51.87
Creatinine levels (mg/dL)	0.3-15.1	1.81 \pm 2.41
Uric acid levels (mg/dL)	0.6-16.6	5.03 \pm 3.17
Sodium levels (mEq/L)	124-164	136.7 \pm 7.15
Potassium levels (mEq/L)	2.9-47	5.05 \pm 5.89
Protein level (g/dL)	3.1-9.4	6.20 \pm 1.34

[Table/Fig-1]: Laboratory parameters of the study population (n=120). SGOT/AST: Aspartate aminotransferase; SGPT/ALT: Alanine transferase; Mean \pm SD was calculated

Antibiotics taken by the patient during the hospital stay	Number of patients (%)
Doxycycline	120
Faropenem	34
Amoxicillin-clavulanic acid	29
Ceftriaxone	19
Cefpodoxime	17
Azithromycin	11
Cefotaxime	11
Leviteracetam	8
Levofloxacin	4
Vancomycin	4
Metronidazole	3
Colistin	3
Minocycline	3

[Table/Fig-2]: Treatment regimen given to scrub typhus patients during hospital stay. Total N=120 study participants

PCT values	Interpretation	Number of scrub typhus patients (n=120) (%)
< 0.05	Normal	8 (6.67%)
0.05- < 0.5	Localised infection possible	46 (38.33%)
0.5- < 2	Systemic bacterial infection possible	30 (25%)
2-10	Systemic bacterial infection likely	19 (15.83%)
> 10	Severe bacterial sepsis, septic shock	17 (14.16%)

[Table/Fig-3]: Values of Procalcitonin (PCT) in scrub typhus reactive patients and interpretation. PCT: Procalcitonin

Parameters	Number of survivors (n=108) (%)	Number of patients who died (n=12) (%)	p-value
Hospital stay of > 7 days	24 (22.2)	9 (75)	0.001
Haemoglobin value (g/dL)	50 (46.2)	8 (66.6)	0.28
Abnormal leucocyte count (cells/ mm^3)	41 (37.9)	5 (41.6)	0.05
Elevated platelet count (platelets/ μL)	2 (1.8)	1 (8.3)	0.23
Elevated alkaline phosphatase (U/L)	56 (51.8)	9 (75)	0.21
Elevated SGOT/AST levels (U/L)	56 (51.8)	12 (100)	0.04
Elevated SGPT/ALT levels (U/L)	50 (46.3)	10 (83.3)	0.04
Elevated amylase levels (U/L)	21 (19.4)	5 (41.6)	0.11

Elevated Total bilirubin count (mg/dL)	45 (41.6)	3 (25)	0.19
Elevated PT value (seconds)	60 (55.5)	12 (100)	0.05
Elevated INR value	59 (54.6)	12 (100)	0.04
Elevated APTT value (seconds)	62 (57.4)	7 (58.3)	0.81
Elevated urea levels (mg/dL)	43 (39.8)	12 (100)	0.01
Elevated creatinine levels (mg/dL)	38 (35.1)	6 (50)	0.42
Elevated uric acid levels (mg/dL)	18 (16.6)	7 (58.3)	0.003
Elevated sodium levels (mEq/L)	1 (0.9)	3 (25)	0.003
Elevated potassium levels (mEq/L)	1 (0.9)	0	0.55
Elevated protein levels (g/dL)	1 (0.9)	2 (16.6)	0.01

[Table/Fig-4]: Comparison of laboratory parameters in survivor and non-survivor scrub typhus patients. SGOT/AST: Aspartate aminotransferase; SGPT/ALT: Alanine transferase; PT: Prothrombin time; INR: International normalised ratio; APTT: Activated partial thromboplastin time; p-value was calculated for statistical significance; Test-applied-Chi-square test, level of significance; p-value of <0.05

From [Table/Fig-4], it can be observed that parameters of liver function tests like SGPT and SGOT, and renal function tests are significantly associated. Hepatic and renal dysfunction are major contributors to morbidity in scrub typhus patients with elevated PCT values. Coagulopathy was also found to be significantly associated (p-value- 0.05) with morbidity in these patients.

DISCUSSION

PCT has been identified as a biomarker for infections of bacterial origin. However, research has shown that it can be elevated in other conditions such as malaria [14], trauma [15], surgery [16], pancreatitis [17], and burns [18]. It has also been used to differentiate between diseases like bacterial pneumonia, tuberculosis, and *Pneumocystis jirovecii* in patients with HIV presenting with community-acquired pneumonia [19]. In this study, the authors aimed to evaluate the significance of PCT levels in scrub typhus patients.

Present study findings indicate that PCT was elevated in a significant proportion of patients with severe scrub typhus infection (n=112; 93.33%). Similar findings were documented in the literature by Peter JV et al., (n=59; 70.2%) [20]. Patients with bacteremia at presentation were excluded, suggesting that high PCT levels in scrub typhus occur independent of co-existent bacterial sepsis.

In this study, increased leukocyte values, elevated liver enzymes like SGOT/AST and SGPT/ALT, abnormal coagulation profile, and abnormal renal profile with elevated urea and uric acid levels were found to be significantly associated with mortality in scrub typhus patients with elevated PCT values. A similar pattern of laboratory parameters was observed in a study by Gaba S et al., [2]. They found that urea, creatinine, bilirubin, and aspartate transaminase levels were significantly higher in the mortality group. Alanine transaminase was higher and albumin was lower in the mortality group, but the differences were not statistically significant. Acute renal injury was present in 27.8% of the patients, liver dysfunction in 90.9%, and one patient had acute liver failure.

Another study from Meghalaya by Sivarajan S et al., reported that elevated SGOT/AST, SGPT/ALT, and creatinine levels were found in 100%, 94%, and 14% of the patients, respectively [21]. A study from Rajasthan by Takhar RP et al., in which the mortality among scrub typhus patients was 21.2%, found elevated transaminases in 48.5% and renal dysfunction in 51.5% of the cases [22]. Elevated liver enzymes have been associated with poor prognosis in patients with scrub typhus [6,8,23]. Abnormal renal profile has also been found to be significant in scrub typhus patients, as supported by several findings documented in the literature [7,9]. Coagulopathy has also been associated with scrub typhus patients with elevated PCT values, as reported by Li W et al., and Lee HJ et al., [24,25].

Furthermore, the worst outcome in scrub typhus patients was associated with elevated PCT levels. In the current study, all 12

patients who died during the study period had elevated PCT levels. Mortality among scrub typhus patients with elevated PCT values was also documented in the study by Peter JV et al., [20]. This study provides evidence that PCT is elevated in critically ill patients with scrub typhus infection and may be associated with a poorer prognosis. Further studies can be conducted in this field to explore the effect of a combination of biomarkers on scrub typhus patients. PCT estimation at the time of admission may be of prognostic value, along with other factors.

Limitation(s)

There are several factors that might affect PCT values, including age, gender, body mass index, smoking, presence of renal failure, and previous sepsis. These factors should be taken into consideration when analysing the results. Although the Scrub typhus IgM ELISA method used in this study for detection has good sensitivity and specificity, the indirect Immunofluorescent Antibody (IFA) assay is considered the gold standard assay.

CONCLUSION(S)

Elevated PCT values were observed in majority of scrub typhus patients and levels higher than 10 were associated with a higher mortality. Hepatic and renal dysfunction were observed in patients with elevated PCT levels. Monitoring these laboratory parameters would help improve the prognosis of patients with scrub typhus and reduce mortality.

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