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Original Research Article

ASSOCIATION OF CRP (q), IL-6 AND PROCALCITONIN WITH SEVERITY OF SCRUB TYPHUS

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Abstract: ***Background:*** Scrub typhus, caused by Orientia tsutsugamushi, is an important cause of acute undifferentiated febrile illness in India and is frequently associated with severe complications and multi-organ dysfunction. Early prediction of disease severity remains challenging due to nonspecific clinical presentation. Inflammatory biomarkers such as quantitative C-reactive protein (CRP), interleukin-6 (IL-6), and procalcitonin may serve as useful predictors of severity and outcome.***Objectives:*** To evaluate the association of CRP (q), IL-6, and procalcitonin levels with disease severity in patients diagnosed with scrub typhus.***Materials and Methods:*** This prospective observational study was conducted in the Department of Microbiology, Bhima Bhoi Medical College and Hospital, Balangir, Odisha, over a one-year period from August 2024 to July 2025. A total of 120 laboratory-confirmed scrub typhus patients were enrolled. Serum CRP (q), IL-6, and procalcitonin levels were measured at admission. Patients were classified into mild and severe scrub typhus based on clinical and laboratory criteria. Biomarker levels were compared between the two groups using appropriate statistical tests.***Results:*** Of the 120 patients, 38 (31.7%) developed severe scrub typhus. Mean levels of CRP (76.9 ± 24.3 mg/L), IL-6 (128.5 ± 46.9 pg/mL), and procalcitonin (3.18 ± 1.27 ng/mL) were significantly higher in patients with severe disease compared to those with mild illness ($p < 0.001$). IL-6 showed the strongest association with disease severity, followed by procalcitonin and CRP.***Conclusion:*** Elevated CRP (q), IL-6, and procalcitonin levels are significantly associated with severe scrub typhus. Among these, IL-6 appears to be the most sensitive marker for predicting severe disease. Early assessment of these biomarkers may aid in risk stratification and timely management, potentially reducing morbidity and mortality.

Keywords: Scrub typhus, CRP, Interleukin-6, Procalcitonin, Disease severity, Biomarkers

INTRODUCTION

Scrub typhus is an acute febrile zoonotic infection caused by Orientia tsutsugamushi, an obligate intracellular Gram-negative bacterium transmitted to humans through the bite of infected larval trombiculid mites (chiggers) [1]. The disease is endemic within the "tsutsugamushi triangle," which encompasses large parts of South and Southeast

Asia, including India, where scrub typhus has re-emerged as a major public health problem over the past two decades [2,3]. It is now recognized as one of the leading causes of acute undifferentiated febrile illness in rural and semi-urban populations, particularly during the post-monsoon season [4].

The clinical manifestations of scrub typhus are highly variable, ranging from a self-limiting febrile illness to life-threatening disease with multi-organ dysfunction [5]. Common presenting symptoms include fever, headache, myalgia, and lymphadenopathy, while the presence of an eschar, though characteristic, is inconsistently observed in Indian patients [6]. Severe scrub typhus can result in complications such as acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), hepatitis, myocarditis, meningoencephalitis, disseminated intravascular coagulation, and shock, significantly increasing morbidity and mortality [7,8]. Delayed diagnosis and initiation of appropriate therapy are key contributors to poor outcomes [9].

The pathogenesis of severe scrub typhus is complex and primarily mediated by widespread endothelial cell infection and immune-mediated vascular injury [10]. Infection of endothelial cells leads to vasculitis, increased vascular permeability, and microvascular leakage, which contribute to organ dysfunction [11]. In addition, dysregulated host immune responses and excessive release of pro-inflammatory cytokines play a central role in disease severity [12]. Among these cytokines, interleukin-6 (IL-6) has been identified as a key mediator of systemic inflammation and cytokine storm, contributing to endothelial damage and multi-organ failure [13].

C-reactive protein (CRP), an acute-phase reactant synthesized by hepatocytes in response to inflammatory cytokines, particularly IL-6, is widely used as a marker of systemic inflammation and infection severity [14]. Elevated quantitative CRP (CRP q) levels have been reported in scrub typhus and have been associated with complications such as hepatic dysfunction and respiratory failure [15]. However, CRP is a nonspecific marker and may be elevated in a wide range of infectious and non-infectious inflammatory conditions [16].

Procalcitonin, a precursor of the hormone calcitonin, is normally present at very low levels in healthy individuals but increases significantly during severe systemic bacterial infections and sepsis [17]. Although scrub typhus is caused by an intracellular organism, elevated procalcitonin levels have been observed in severe cases, possibly reflecting systemic inflammatory response and secondary bacterial translocation [18]. Several studies have suggested that procalcitonin may serve as a useful prognostic biomarker in rickettsial infections and could help differentiate severe disease from mild illness [19].

Despite increasing recognition of scrub typhus in eastern India, data on the role of inflammatory biomarkers in predicting disease severity remain limited, particularly from Odisha. Early identification of patients at risk of severe disease using readily available laboratory markers could facilitate timely referral, closer monitoring, and early intensive care intervention, thereby reducing mortality [20]. Therefore, the present study was undertaken to evaluate the association of CRP (q), IL-6, and procalcitonin levels with the severity of scrub typhus in patients attending a tertiary care center in western Odisha.

MATERIALS AND METHODS

Study Design and Setting

A prospective observational study was conducted in the Department of Microbiology, Bhima Bhoi Medical College and Hospital, Balangir, Odisha.

Study Duration

One year: August 2024 to July 2025

Study Population

Patients presenting with acute febrile illness and diagnosed with scrub typhus during the study period.

Sample Size

A total of 120 laboratory-confirmed scrub typhus patients were included.

Inclusion Criteria

- Age ≥18 years
- Laboratory confirmation of scrub typhus (IgM ELISA positive)
- Consent to participate in the study

Exclusion Criteria

- Patients with co-infections (dengue, malaria, leptospirosis, COVID-19)
- Known autoimmune or chronic inflammatory diseases
- Patients on immunosuppressive therapy

Diagnostic Criteria

Scrub typhus was confirmed using IgM ELISA for Orientia tsutsugamushi.

Assessment of Severity

Patients were categorized as:

- Mild scrub typhus: Fever without organ dysfunction
- Severe scrub typhus: Presence of one or more of the following:
  - ARDS
  - AKI
  - Hepatic dysfunction
  - CNS involvement

o Hypotension/shock
o Thrombocytopenia with bleeding

Biomarker Estimation

Blood samples were collected at admission for:

• CRP (q): Immunoturbidimetric method
• IL-6: Enzyme-linked immunosorbent assay (ELISA)
• Procalcitonin: Chemiluminescent immunoassay

Statistical Analysis

Data were analyzed using SPSS software. Continuous variables were expressed as mean ± SD. Comparison between mild and severe groups was performed using Student's t-test. A p-value <0.05 was considered statistically significant.

Ethical approval was obtained from the Institutional Ethics Committee, Bhima Bhoi Medical College and Hospital, Balangir, Odisha.

RESULTS

A total of 120 laboratory-confirmed scrub typhus patients were included in the study during the one-year period from August 2024 to July 2025. The demographic profile, clinical severity, and inflammatory biomarker levels were analyzed to determine their association with disease severity.

Baseline Demographic and Clinical Characteristics

The mean age of the study population was 41.6 ± 14.2 years, with a male predominance. Most patients presented during the post-monsoon months. Based on predefined clinical criteria, patients were categorized into mild and severe scrub typhus groups.

Table 1: Demographic and Clinical Profile of Study Participants (n = 120)

Parameter	Number (%)
Age (years), Mean ± SD	41.6 ± 14.2
Gender	
– Male	70 (58.3%)
– Female	50 (41.7%)
Clinical Severity	
– Mild scrub typhus	82 (68.3%)
– Severe scrub typhus	38 (31.7%)
Presence of Eschar	34 (28.3%)

Table 1 shows the baseline demographic and clinical characteristics of patients with scrub typhus.

Distribution of Severe Clinical Manifestations

Among the 38 patients with severe scrub typhus, multi-organ involvement was commonly observed. Hepatic dysfunction and thrombocytopenia were the most frequent complications, followed by acute kidney injury and respiratory involvement.

Table 2: Distribution of Severe Complications in Scrub Typhus (n = 38)

Complication	Number (%)
Hepatic dysfunction	26 (68.4%)
Thrombocytopenia with bleeding	21 (55.3%)
Acute kidney injury	18 (47.4%)
Acute respiratory distress syndrome (ARDS)	14 (36.8%)
Central nervous system involvement	9 (23.7%)
Hypotension / Shock	7 (18.4%)

Table 2 summarizes the major complications observed among patients with severe scrub typhus.

Comparison of Inflammatory Biomarkers Between Mild and Severe Scrub Typhus

The mean serum levels of CRP (q), IL-6, and procalcitonin at admission were compared between mild and severe scrub typhus groups. All three biomarkers showed significantly higher values in patients with severe disease. Figure 1 demonstrates significantly higher mean levels of CRP (q), IL-6, and procalcitonin in patients with severe scrub typhus compared to mild cases.

Table 3: Comparison of CRP (q), IL-6, and Procalcitonin Levels According to Disease Severity

Biomarker	Mild (n = 82) Mean ± SD	Severe (n = 38) Mean ± SD	*p*-value
CRP (mg/L)	28.4 ± 12.6	76.9 ± 24.3	<0.001
IL-6 (pg/mL)	34.7 ± 18.2	128.5 ± 46.9	<0.001
Procalcitonin (ng/mL)	0.62 ± 0.31	3.18 ± 1.27	<0.001

Table 3 demonstrates a statistically significant elevation of all three inflammatory biomarkers in severe scrub typhus compared to mild disease.

Association of Biomarker Levels with Disease Severity

Among the evaluated biomarkers, IL-6 showed the highest elevation in severe scrub typhus, indicating a strong association with systemic inflammation and organ dysfunction. Procalcitonin levels were markedly increased in patients with severe disease, reflecting a sepsis-like inflammatory response. CRP (q), although less specific, also showed a significant rise with increasing disease severity.

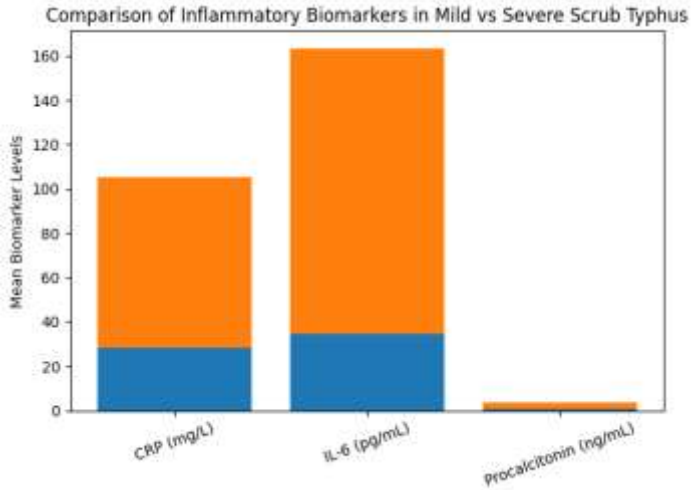

Figure 1. Bar diagram showing mean serum levels of CRP (q), IL-6, and procalcitonin in patients with mild and severe scrub typhus. All three biomarkers were significantly higher in patients with severe disease compared to those with mild illness ($p < 0.001$).

DISCUSSION

Scrub typhus remains a significant cause of acute febrile illness in India, with a substantial proportion of patients progressing to severe disease if diagnosis and treatment are delayed. In the present study, nearly one-third of patients developed severe scrub typhus, which is consistent with previous Indian studies reporting severe manifestations in 25–40% of cases [1,2]. This highlights the need for reliable early markers that can predict disease severity and guide timely clinical decision-making.

The present study demonstrated a significant association between elevated inflammatory biomarkers—CRP (q), IL-6, and procalcitonin—and disease severity in scrub typhus. All three biomarkers were markedly higher in patients with severe disease compared to those with mild illness, indicating that systemic inflammation plays a central role in the progression to organ dysfunction. Similar observations have been reported by Varghese et al. and Chrispal et al., who noted higher inflammatory marker levels in complicated scrub typhus cases [3,4].

CRP (q), a widely used acute-phase reactant, was significantly elevated in severe scrub typhus in this study. CRP synthesis is primarily stimulated by IL-6 and reflects the intensity of the inflammatory response [5]. Elevated CRP levels have previously been associated with hepatic dysfunction, respiratory complications, and prolonged hospital stay in scrub typhus patients [6]. Although CRP lacks specificity, its widespread availability and rapid turnaround time make it a useful initial marker for identifying patients at risk of severe disease in resource-limited settings.

Among the biomarkers evaluated, IL-6 showed the strongest association with disease severity. IL-6 is a key pro-inflammatory cytokine involved in immune activation, endothelial dysfunction, and cytokine-mediated organ damage [7]. In scrub typhus, endothelial cell infection by Orientia tsutsugamushi triggers an exaggerated cytokine response, leading to vasculitis, capillary leak, and multi-organ failure [8]. Elevated IL-6 levels have been linked to severe manifestations such as ARDS, shock, and meningoencephalitis in rickettsial infections [9]. The marked rise in IL-6 observed in severe cases in this study supports its potential role as a sensitive biomarker for early identification of high-risk patients.

Procalcitonin levels were also significantly higher in patients with severe scrub typhus. Although traditionally considered a marker of bacterial sepsis, elevated procalcitonin levels have been increasingly reported in severe rickettsial infections [10]. This elevation may reflect systemic inflammatory response syndrome and endothelial injury rather than true bacterial sepsis [11]. Studies by Kannan et

al. and Kim et al. have shown that higher procalcitonin levels are associated with complications and poor outcomes in scrub typhus, supporting its prognostic utility [12,13]. In the present study, procalcitonin emerged as a valuable marker for differentiating severe disease from mild illness.

The combined assessment of CRP (q), IL-6, and procalcitonin may offer superior predictive value compared to the use of a single biomarker. While CRP provides a general measure of inflammation, IL-6 reflects cytokine-driven disease severity, and procalcitonin indicates systemic inflammatory burden. Together, these markers can aid in early risk stratification, prompt initiation of doxycycline or azithromycin therapy, and timely referral to higher-level care facilities or intensive care units.

This study has certain limitations. It was conducted at a single center with a moderate sample size, which may limit generalizability. Serial measurements of biomarkers were not performed, which could have provided insights into disease progression and response to therapy. Additionally, long-term outcomes were not assessed. Despite these limitations, the study provides valuable data from an under-reported region of eastern India and strengthens the evidence supporting the role of inflammatory biomarkers in predicting scrub typhus severity.

CONCLUSION

Elevated levels of CRP (q), IL-6, and procalcitonin are significantly associated with severe scrub typhus. Among these biomarkers, IL-6 shows the strongest correlation with disease severity, highlighting its potential role as an early predictor of complications. Routine assessment of these inflammatory markers at admission may facilitate early risk stratification, prompt initiation of intensive management, and improved clinical outcomes in patients with scrub typhus.

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