Uncommon Clinical and Biochemical Presentation of Scrub Typhus - An Observation Study

Keshav Agrawal[1], Saurav Sangwan[1], Hitesh Sharma[1], Nikhil kumar Nehra[2], Vishwanjali Gupta[3],Sunil Kumar Mahavar[4], Puneet Saxena[5]

[1] *Third Year Residents, General Medicine, SMS Hospital, Jaipur*
[2] *Senior Resident, General Medicine, SMS Hospital, Jaipur*
[3] *Second Year Resident, General Medicine, SMS Hospital, Jaipur*
[4] *Professor, General Medicine, SMS Hospital, Jaipur*
[5] *Senior Professor, General Medicine, SMS Hospital, Jaipur*

***Corresponding Author**: Nikhil kumar Nehra**
(Email: nikhilnehra7500@gmail.com)

KEYWORDS
Scrub typhus, Immature platelet fraction (IPF), Peri-gallbladder edema, Prognostic markers, Mortality risk, Public health.

ABSTRACT:
Background: Scrub typhus, a neglected tropical disease, poses a significant threat to public health. Early diagnosis and treatment are crucial to preventing mortality.
Methods: A retrospective study of 240 patients diagnosed with scrub typhus was conducted to analyze the prognostic value of immature platelet fraction (IPF) and peri-gallbladder edema.
Results: Low IPF (<10%) was associated with higher mortality ($p<0.01$), while elevated IPF (>20%) was linked to better outcomes ($p<0.05$). Peri-gallbladder edema was identified as a significant diagnostic marker, with a higher incidence in mortality cases (63.3%, $p<0.001$).
Conclusion: This study highlights the potential of IPF and peri-gallbladder edema as novel prognostic markers in scrub typhus. Low IPF and presence of peri-gallbladder edema may indicate a higher risk of mortality, warranting prompt and aggressive treatment. These findings may aid in the early identification and management of severe cases, ultimately improving patient outcomes

INTRODUCTION

Scrub typhus, one of the three most common causes of prolonged fever in rural Southeast Asia, affects nearly 1 million people annually [1]. This acute febrile, vector-borne zoonotic illness is caused by Orientia tsutsugamushi, a gram-negative intracellular coccobacillus with a tropism for endothelial cells [2]. After infecting host cells, O. tsutsugamushi is released by budding from the plasma membrane and may be phagocytosed by adjacent cells while still coated with its original host cell membranes [2]. The disease has a long history, with the earliest description dating back to 313 AD [1]. However, it wasn't until after World War 2 that scrub typhus emerged as a significant threat, primarily affecting army and naval personnel [1]. The disease is propagated by trombuculid mites (chiggers) and has been categorized as one of the world's most underdiagnosed and underreported diseases by the World Health Organization [3]. Scrub typhus is predominantly a rural disease, with farmers being disproportionately affected, as evident from a comprehensive study in China involving 27,391 cases from 2006 to 2012 [4]. The vector mites thrive in diverse ecological niches, including equatorial rain forests, subarctic terrains, and semi-deserts in the Himalayan regions [5]. In recent decades, the infection has exhibited exponential growth, particularly in India during the cooler months (July to November) [6]. Symptoms typically manifest within 10 days of the bite [7] and may include fever, chills, headache, body aches, muscle pain, abdominal pain, vomiting, mental changes, and enlarged lymph nodes [7]. A distinctive clinical feature of scrub typhus is the presence of a dark, scab-like region at the site of the chigger bite, known as an eschar [7]. Eschars serve as a valuable diagnostic tool, allowing for early detection and

differentiation from other rickettsial infections [8, 9]. The presence of eschars can facilitate the diagnosis of scrub typhus, particularly in resource-limited settings where molecular testing may be challenging [10]. PCR amplification from eschar material has been shown to be an effective method for identifying O. tsutsugamushi, even in cases where serological testing may be inconclusive [11, 12].

MATERIALS AND METHODS

Study Design

This was a retrospective study conducted at a tertiary care hospital in a region endemic for scrub typhus. The study aimed to analyze the demographic and clinical characteristics of scrub typhus patients and identify potential associations with mortality.

Study Population

The study included 240 patients diagnosed with scrub typhus between [insert time period]. Patients were included based on positive serological tests for scrub typhus,like enzyme-linked immunosorbent assay (ELISA).

Data Collection

Demographic and clinical data, including occupation, symptoms, and laboratory results, were collected from patient records. The data collection process was done manually by reviewing patient files and electronic medical records.

Laboratory Tests

Laboratory tests included:

1) Complete Blood Counts (CBC): To evaluate hematological parameters, including platelet count, hemoglobin, and white blood cell count.
2) Liver Function Tests (LFTs): To assess liver damage, including serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT).
3) Renal Function Tests (RFTs): To evaluate kidney function, including serum urea and serum creatinine.
4) Serum Triglyceride Levels: To assess lipid profiles.

Statistical Analysis

Descriptive statistics were used to summarize demographic and clinical data. Chi-square tests and logistic regression analysis were used to identify associations between variables, including occupation, symptoms, laboratory results, and mortality

Rationale for Examining Atypical Markers (IPF and Peri-GB Edema)

Atypical features such as elevated IPF and peri-GB edema can provide additional diagnostic insights, especially in endemic regions where timely and accurate detection of scrub typhus remains challenging. Elevated IPF, a marker of platelet production, is often associated with severe infections or inflammation, which may reflect immune response variations in scrub typhus (Luce-Fedrow et al., 2018) [13]. Similarly, peri-GB edema, though uncommon, has been linked to systemic infections and may indicate an inflammatory response linked to Orientia tsutsugamushi (Kumar et al., 2014) [14].

Need for Enhanced Diagnostic Criteria

Given that scrub typhus is endemic in many regions and can lead to severe complications if undiagnosed, studies focusing on novel markers like IPF and peri-GB oedema can improve diagnostic criteria and treatment outcomes. Such atypical markers might also refine case definitions, making it

easier for clinicians to identify scrub typhus in its early stages when treatment is most effective (Watt & Parola, 2003) [15].

Public Health Impact

Understanding and documenting these new clinical features is crucial for early detection and prevention of complications, especially since scrub typhus can escalate to life-threatening conditions such as acute respiratory distress syndrome (ARDS) and multiple organ failure if untreated (Varghese et al., 2013) [16].

OBSERVATIONS AND RESULTS

A total of 240 cases with confirmed scrub typhus were recorded from May 2024 to November 2024.

Demographic Characteristics of Scrub Typhus Patients-The study population consisted of 240 patients, with a mean age of 44.85 years. The gender distribution was nearly equal, with 118 (49.16%) female patients and 122 (50.83%) male patients (Figure 1).

Geographical Distribution and Occupation-Most patients hailed from rural and semi-urban areas, including Tonk, Karauli, Sawai Madhopur, and Bundi, with some contributions from urban areas like Jaipur, Alwar, and Sikar. In terms of occupation, 43% (n=105) of patients were farmers, followed by homemakers (n=73), students (n=27), labourers (n=3), business professionals (n=4), and retired individuals (n=2).

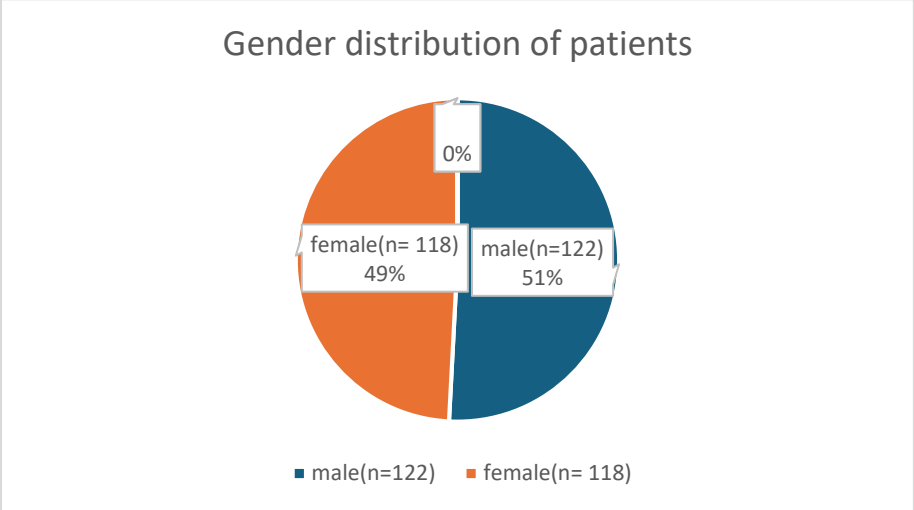

Figure 1. Gender distribution of patients

Patients presented to the institute within a timeframe of 3-18 days after the onset of illness (Figure 2), exhibiting a diverse range of symptoms. The most prevalent symptom was fever, which was observed in all patients (100%, n=240). Other common symptoms included headache (61.66%, n=148), shortness of breath (42.5%, n=101), and nausea/vomiting (20%, n=49). Additionally, a significant proportion of patients experienced pain abdomen (22.5%, n=54), myalgia (muscle pain) (22.5%, n=54), and rash (15%, n=38). Notably, altered sensorium was observed in 9.1% (n=22) of patients, while diarrhoea was reported in only 1.25% (n=3) of cases. Interestingly, redness of eyes emerged as a new symptom in scrub typhus, affecting 18.3% (n=44) of patients.This finding highlights the evolving nature of scrub typhus and the importance of continued surveillance and research.

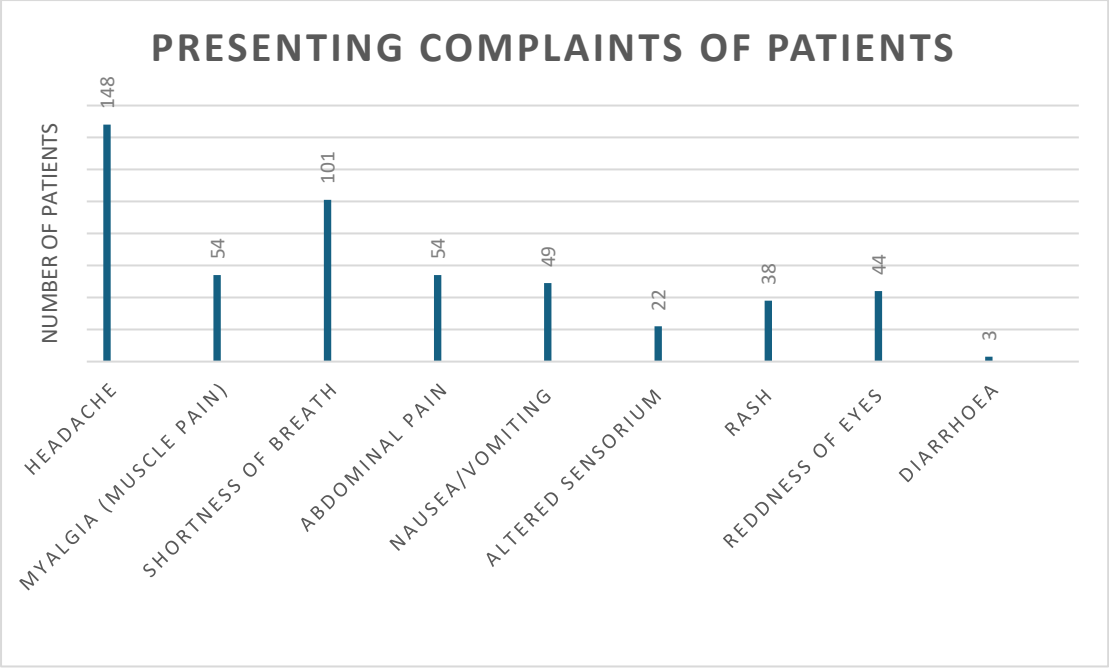

Figure 2. PRESENTING COMPLAINTS OF PATIENTS

Clinical and Laboratory Findings

Eschar, a characteristic skin lesion, was observed in 38 (15%) patients, predominantly located on the lower extremities. Haematological analysis revealed thrombocytopenia (platelet count <= 1 lakh) in 179 cases. The remaining patients had platelet counts above 1 lakh.

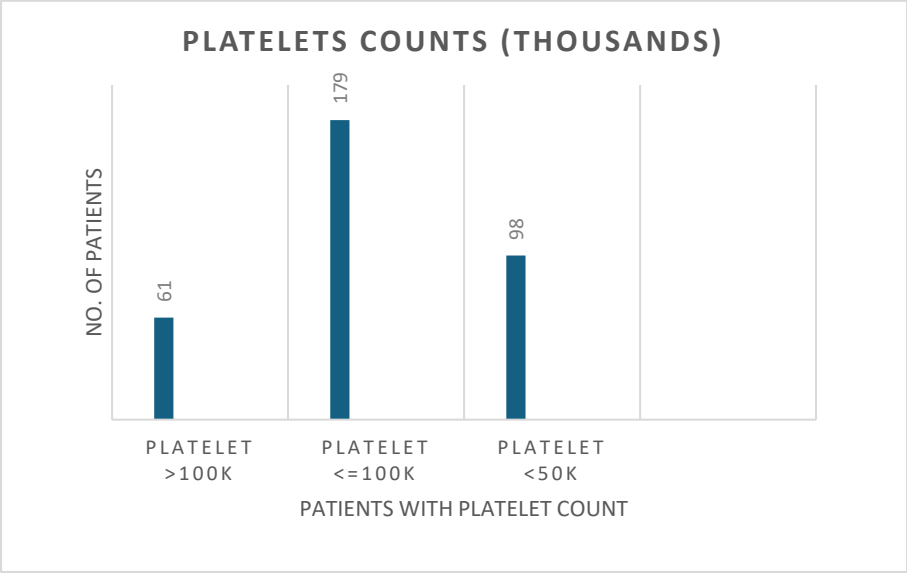

Figure 3. PLATELETS COUNTS IN PATIENTS

Mortality Association with Low Platelet Count-A striking correlation was observed between low platelet count and mortality. Among the 30 mortality cases recorded, a significant proportion (93.3%) had platelet counts less than 100,000/µL. Moreover, 20 (66.7%) of these patients had critically low platelet counts less than 50,000/µL. This finding underscores the critical importance of platelet count as a prognostic indicator in scrub typhus. The association between low platelet count and increased

mortality risk highlights the need for prompt recognition and management of thrombocytopenia in patients with scrub typhus.

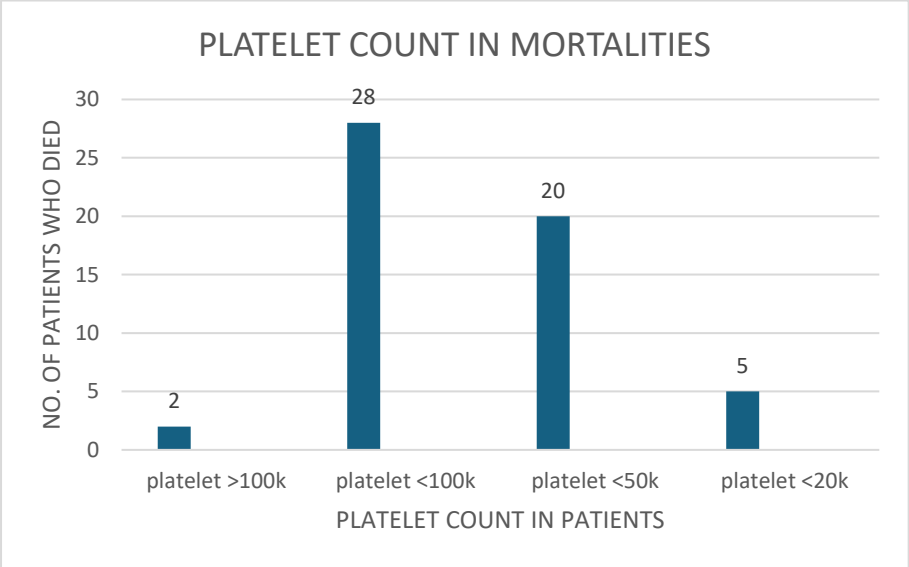

Figure 4. PLATELET COUNT AMONG MORTALITIES

Immature Platelet Fraction (IPF) Analysis in Scrub Typhus Patients

Among 240 patients diagnosed with scrub typhus, elevated IPF levels (≥9) were observed in 149 (62.08%) patients, while 91 (37.91%) patients had IPF levels ≤9.Notably, a significant disparity was observed in IPF levels among mortality cases. Among 30 fatalities, IPF was elevated (≥9) in only 11 (36.66%) patients, whereas 19 (63.33%) patients had IPF levels ≤9.

Conclusion:- This study reveals a critical association between low platelet count, low Immature Platelet Fraction (IPF), and higher mortality in scrub typhus patients. The findings suggest that patients with thrombocytopenia (low platelet count) and low IPF levels are at increased risk of mortality. This combination of factors may serve as a predictive marker for poor prognosis in scrub typhus patients. The observed disparity in IPF levels among mortality cases highlights the importance of monitoring IPF levels in patients with scrub typhus. Early identification of patients with low IPF levels may enable timely intervention and potentially improve outcomes. Furthermore, this study underscores the need for a comprehensive understanding of the pathophysiological mechanisms underlying scrub typhus. Elucidating the relationships between platelet count, IPF, and mortality may inform the development of novel therapeutic strategies and improve patient care.

Hematological Profile:

Total Leukocyte Count (TLC)-The total leukocyte count (TLC) was evaluated in the study population to assess the immune response and potential inflammation associated with scrub typhus. The results revealed a varied distribution of TLC values among the patients.Specifically, 19 (7.91%) patients had a TLC of less than 4,000 cells/μL, indicating leukopenia, which may be indicative of a compromised immune system or bone marrow suppression. In contrast, 127 (52.91%) patients had a TLC within the normal range of 4,000-11,000 cells/μL, suggesting an intact immune response.Interestingly, 94 (39.17%) patients had a TLC of greater than 11,000 cells/μL, indicating leukocytosis, which may be indicative of an inflammatory response or infection. This finding suggests that scrub typhus may trigger a significant inflammatory response in some patients, which may contribute to the disease's pathogenesis and severity.

Haemoglobin Levels- A comprehensive analysis of haemoglobin levels was conducted among patients diagnosed with scrub typhus. The results revealed a striking prevalence of anaemia in this population. Among the 240 patients studied, 185 (77.08%) had haemoglobin levels less than 12 gm/dl, indicating anaemia. This finding suggests that anaemia is a common comorbidity among patients with scrub typhus. Furthermore, a significant association was observed between anaemia and mortality. Among the 30 mortality cases, 26 (86.66%) patients were found to be anaemic, with haemoglobin levels less than 12 gm/dl. In contrast, only 4 (13.33%) patients had haemoglobin levels greater than 12 gm/dl. This disparity highlights the critical role of anaemia in contributing to the severity and outcome of scrub typhus. The high prevalence of anaemia among scrub typhus patients may be attributed to various factors, including chronic inflammation, bone marrow suppression, and haemolysis. The presence of anaemia may exacerbate the disease's severity by compromising oxygen delivery to tissues, impairing immune function, and increasing the risk of organ dysfunction. In conclusion, the study's findings underscore the importance of anaemia as a prognostic factor in scrub typhus. Early identification and management of anaemia are crucial to improving outcomes and reducing mortality risk in patients with scrub typhus. Healthcare providers should prioritize the diagnosis and treatment of anaemia in these patients to optimize their care.

Liver Function Tests Renal Parameters and other Biochemical and Radiological Parameters

A comprehensive analysis of liver function tests and renal parameters was conducted among patients diagnosed with scrub typhus.

Liver Function Tests

Significant liver dysfunction was observed in scrub typhus patients. Elevated serum glutamic-oxaloacetic transaminase (SGOT) (>35 u/l) was found in 204 (85%) patients, while elevated serum glutamic-pyruvic transaminase (SGPT) (>40 u/l) was observed in 197 (82.08%) patients.

Notably, among mortality cases, both SGOT and SGPT levels were significantly higher compared to patients who recovered. This finding suggests that liver dysfunction may play a critical role in the severity and outcome of scrub typhus.

Renal Parameters

Renal parameters also showed significant abnormalities. Elevated serum urea was found in 112 (46.66%) patients, while elevated serum creatinine was observed in 82 (34.16%) patients.

Among mortality cases, a higher proportion of patients had elevated serum urea, with 24 out of 30 patients (80%) exhibiting this abnormality. Similarly, 23 out of 30 patients (76.6%) had elevated serum creatinine levels. This finding suggests that renal dysfunction may be a contributing factor to the increased mortality risk observed in scrub typhus patients.

Lipid Profile: Serum Triglycerides

Hypertriglyceridemia was commonly observed in scrub typhus patients. Among 118 female patients, 91 (77.11%) had elevated serum triglycerides (>140 mg/dl), while among 122 male patients, 74 (60.66%) had elevated serum triglycerides (>165 mg/dl).Notably, among mortality cases, the incidence of hypertriglyceridemia was even higher. Among 30 mortality cases (13 female, 17 male), 27 out of 30 patients (90%) had hypertriglyceridemia, including:

12 out of 13 female patients (92.3%) with elevated serum triglycerides (>140 mg/dl)

15 out of 17 male patients (88.2%) with elevated serum triglycerides (>165 mg/dl)

This finding suggests that hypertriglyceridemia is a common feature in scrub typhus patients and may be associated with increased mortality risk.

Serum Ferritin Levels

Serum ferritin levels were evaluated in 184 out of 240 patients diagnosed with scrub typhus. The normal range for serum ferritin is 22-322 mg/dl for males and 10-290 mg/dl for females.The results showed that 59 male patients (32.06% of the 184 patients) had elevated serum ferritin levels (>322 mg/dl), while 45 female patients (24.46% of the 184 patients) had elevated serum ferritin levels (>290 mg/dl). Overall, 104 patients (56.52% of the 184 patients) had elevated serum ferritin levels.

Peri-Gallbladder Oedema on abdominal sonography

An interesting finding was observed in scrub typhus cases, where peri-gallbladder oedema, a previously uncommon feature, was found to have an increased incidence. Out of 240 patients, 84 (35% of cases) had peri-gallbladder oedema.

Notably, the incidence of peri-gallbladder oedema was significantly higher among mortality cases. Out of 30 mortality cases, 19 (63.33%) had peri-gallbladder oedema, indicating a potential association between this feature and increased mortality risk in scrub typhus patients.

CONCLUSION

This comprehensive study provides a detailed analysis of the demographic and clinical characteristics of scrub typhus patients in a specific region. The findings highlight the importance of understanding the local epidemiology and clinical presentation of scrub typhus to improve diagnosis and treatment outcomes.

Key Findings

1) Occupational and demographic characteristics: Farmers were the most commonly affected occupation (43%), and homemakers accounted for 61.86% of female patients.
2) Clinical presentation: Fever, headache, and myalgia were common symptoms, while redness of eyes emerged as a new symptom warranting further investigation.
3) Laboratory findings: Thrombocytopenia (72.91%), elevated immature platelet fraction (IPF) (62.08%), anaemia (77.8%), elevated liver enzymes (SGOT and SGPT) (85% and 82.08%, respectively), and hypertriglyceridemia (77.11% of female patients and 74.59% of male patients) were significant laboratory findings.
4) Association with mortality: Low platelet count along with low IPF was associated with higher mortality in scrub-positive patients.
5) Diagnostic marker: Peri-gallbladder oedema emerged as a significant diagnostic marker, with a higher incidence in mortalities.

Implications

This study provides valuable insights into the clinical and laboratory characteristics of scrub typhus patients, highlighting the need for:

1) Early diagnosis and treatment to prevent mortality.
2) Increased awareness among healthcare professionals about the local epidemiology and clinical presentation of scrub typhus.
3) Further research into the pathogenesis and treatment of scrub typhus.

Study Limitations

Retrospective Design

The retrospective design of the study may have introduced bias in the selection of patients and the collection of data. This design relies on existing data, which may be incomplete, inaccurate, or influenced by various biases.

Limited Sample Size
The sample size of 240 patients may not be representative of the entire population of scrub typhus patients. A larger sample size would have provided more robust results and increased the generalizability of the findings.

Lack of Control Group
The study did not include a control group, which would have allowed for comparisons between scrub typhus patients and healthy individuals. This would have helped to identify specific characteristics and risk factors associated with scrub typhus.

Limited Geographic Representation
The study was conducted in a single region, which may not be representative of other regions where scrub typhus is endemic. Scrub typhus has varying epidemiological characteristics across different regions, and this study's findings may not be generalizable to other areas.

Potential for Selection Bias
The study included only patients who were diagnosed with scrub typhus, which may have introduced selection bias. Patients with mild or asymptomatic cases may not have been included in the study, potentially leading to an overestimation of the severity of the disease.

Limited Follow-up Data
The study did not include follow-up data on patient outcomes, which would have allowed for an analysis of the long-term effects of scrub typhus. This would have provided valuable insights into the disease's natural history and the effectiveness of treatment interventions.

Reliance on Existing Data
The study relied on existing data from patient records, which may have been incomplete or inaccurate. This may have introduced biases and limitations in the analysis, particularly if the data was not consistently recorded or was influenced by various biases.

REFERENCES

1. Sharma R, Gupta M, Mahavar SK, Agarwal M. Scrub typhus: as it stands today. Int J Res Med Sci 2019;7:3605-9.
2. Atwal S, Wongsantichon J, Giengkam S, Saharat K, Pittayasathornthun YJ, Chuenklin S, et al. The obligate intracellular bacterium Orientia tsutsugamushi differentiates into a developmentally distinct extracellular state. Nat Commun 2022;13(1):3603.
3. World Health Organization. WHO Recommended Surveillance Standards. Geneva (Switzerland): World Health Organization; 1999.
4. Zhang WY, Wang LY, Ding F, Hu WB, Soares Magalhaes RJ, Sun HL, et al. Scrub typhus in mainland China, 2006-2012: the need for targeted public health interventions. PLoSNegl Trop Dis 2013;7(12):e2493.
5. Chakraborty S, Sarma N. Scrub Typhus: An Emerging Threat. Indian J Dermatol 2017;62(5):478-85.
6. Panda S, Swain SK, Sarangi R. An epidemiological outbreak of scrub typhus caused by Orientia tsutsugamushi – A comprehensive review. J App Biol Biotech 2022;10(5):76-83.
7. Centers for Disease Control and Prevention. Scrub Typhus. [Cited 2022]. Available from: (link unavailable).
8. Charles CH, Whitman TJ. Eschar-associated rickettsial infections. Infect Dis Clin North Am 2009;23(3):451-64.

9. Luce-Fedrow A, Lehman ML, Kelly DJ, Mullins K, Maina AN, Stewart RL, et al. A Review of Scrub Typhus (Orientia tsutsugamushi and Related Organisms): Then, Now, and Tomorrow. Trop Med Infect Dis 2018;3(1):8.
10. Chogle AR. Diagnosis and Treatment of Scrub Typhus – The Indian Scenario. J Assoc Physicians India 2010;58:11-2.
11. Liu YX, Feng D, Zhang Q, Jia N, Yang ZQ, Fan Y
12. Sharma R, Gupta M, Mahavar SK, Agarwal M. Scrub typhus: as it stands today. Int J Res Med Sci 2019;7:3605-9.
13. Luce-Fedrow A, Lehman ML, Kelly DJ, Mullins K, Maina AN, Stewart RL, et al. A Review of Scrub Typhus (Orientia tsutsugamushi and Related Organisms): Then, Now, and Tomorrow. Trop Med Infect Dis 2018;3(1):8.
14. Kumar B, et al. Hepatic and biliary involvement in scrub typhus. J Assoc Physicians India 2014;62(11):957-62.
15. Watt G, Parola P. Scrub typhus and tropical rickettsioses. Curr Opin Infect Dis 2003;16(5):429-36.
16. Varghese GM, et al. Clinical profile and improving mortality trend of scrub typhus in South India. Int J Infect Dis 2013;17(11).