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Original Research Article

A Study of Scrub Typhus in a Tertiary Care Hospital in the Southern Region of Rajasthan, India

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Abstract:

Background: Scrub typhus is a zoonotic rickettsial infection caused by an intracellular gram negative bacterium Orientia tsutsugamushi, transmitted through bites of larval leptotrombiculid mites. The nonspecific clinical presentations, including fever, rash, headache, nausea, vomiting, and thrombocytopenia, pose a significant diagnostic challenge due to overlapping symptoms with other infections like malaria, chikungunya, dengue, enteric fever, leptospirosis, brucellosis, and malaria.

Aims & Objectives: The present study aimed to assess the severity profile of diagnosed patients of scrub-type infection specifically within a hospital in Southern region of Rajasthan, India.

Methodology: A hospital-based prospective analytical study was carried out from November 2020 to November 2023 at Pacific Institute of Medical Sciences, Udaipur, Rajasthan.

Results: A total of 350 confirmed cases of scrub type were enrolled in the study. The highest number of patients were seen in the age group of between 41 - 50 years 103 patients (29.42%), this was followed by age groups of 31 - 40 years with patients of 95 (27.14%), 21 - 30 years 41 patients (11.71%), 51 - 60 years and 61 - 70 years each had 32 patients (9.14%). Hepatomegaly was recorded in 144 (41.14%) of the patients, splenomegaly in 145 (41.42%) patients, and lymphadenopathy was noted in 29.71% of the study population. The level of liver enzymes such as SGPT (33.14%), and SGOT (32%) and raised level of blood urea (24.85%), serum creatinine (25.42%) were significantly associated with ST (p-value 0.01). The most common clinical symptoms were fever (100%), headache (88.57%), myalgia (98%), rashes (75.14%), breathing difficulty (63.14%) and conjunctival suffusion (10.57%). The pathognomonic eschar was observed in 83 (23.71%) of the patients.

Conclusion: Scrub typhus has emerged as an important cause of febrile illness in the southern region of Rajasthan and can present with varying clinical manifestations with or without eschar. Early laboratory diagnosis and prompt intervention may help in reducing the case fatality.

Keywords: Scrub Typhus, Severity, Clinical Features, Eschar.

Introduction

Rickettsial infections are experiencing a resurgence worldwide, with scrub typhus being a prominent zoonotic rickettsial infection caused by an intracellular gram negative bacterium Orientia tsutsugamushi, transmitted through bites of larval leptotrombiculid mites. Scrub typhus was first described by Hashimoto from Japan in 1899. [1] The term "scrub" in scrub typhus refers to the type of vegetation where the vector is found, but it's not entirely accurate as endemic areas can also include sandy, semi-arid, and mountainous desert regions. [2,3] The endemic nature of scrub typhus is highlighted by its prevalence in the "tsutsugamushi triangle," spanning from Japan and Russia in the north to Australia in the south and Pakistan in the west, making it a significant pathogen in the Asia-Pacific region, contributing up to 23% of febrile episodes. [4,5] Globally over one billion people are at risk for scrub typhus and an estimated one million cases occur annually. In India, recent trends indicate a resurgence of scrub typhus in various states including Maharashtra, Tamil Nadu, Karnataka, Kerala, Jammu and Kashmir, Uttaranchal, Himachal Pradesh, Rajasthan, Assam, and West Bengal, challenging its previous status as a neglected disease. Rajasthan, characterized by

monsoons and vegetation with average temperatures conducive to the spread of scrub typhus vectors, faces a heightened risk during these periods, creating an optimal environment for disease transmission. [6,7,8,9,10,11]

After an incubation period of 6 to 21 days, typically around 10 to 12 days, scrub typhus manifests with flu-like symptoms. This includes fever, rash, headache, and the development of eschar. In some cases, patients may also experience pneumonitis, leading to severe systemic multi-organ failure if left untreated. This failure can involve renal dysfunction, respiratory issues, and CNS complications. [12,13,14]

The nonspecific clinical presentations of scrub typhus, including fever, rash, headache, nausea, vomiting, and thrombocytopenia, pose a significant diagnostic challenge due to overlapping symptoms with other infections like malaria, chikungunya, dengue, enteric fever, leptospirosis, and brucellosis. Furthermore, scrub typhus can progress to life-threatening complications such as pneumonitis, meningoencephalitis, hyperbilirubinemia, renal failure, and myocarditis, leading to a spectrum of mild to severe manifestations, including multiorgan failure and death. [15]

Untreated cases of scrub typhus have shown case fatality rates ranging from 3% to 60%, emphasizing the critical need for early diagnosis and appropriate treatment to prevent severe outcomes. [16,17]

The absence of licensed vaccines, unreliable diagnostic tools, and inadequate vector management strategies have contributed to an increasing number of severe scrub typhus cases, resulting in poor clinical outcomes. Recent trends and reports from the southern region of Rajasthan also underscore the substantial mortality caused by scrub typhus, highlighting the urgent need for effective surveillance, diagnosis, and management strategies in endemic areas. Against this backdrop, the present study aimed to assess the severity profile of diagnosed scrub typhus patients specifically within a tertiary care hospital in Southern region of Rajasthan, India.

Material and Methods

Study Design & Sample Size: A hospital-based prospective, analytical study was carried out from November 2020 to November 2023. A total of 350 confirmed scrub typhus positive patients were enrolled in the study. Blood samples were collected from the following participants: all age groups having acute under diagnosed febrile illness patients (axillary temperature >38 C) attending the outpatient department and/or admitted in Pacific Institute of Medical Sciences (PIMS) Udaipur, Rajasthan.

Inclusion Criteria: All age group patients with acute under diagnosed febrile illness presenting with or without eschar in our hospital were included in the study.

Exclusion Criteria: All other patients with tropical illness, such as dengue, typhoid fever, leptospirosis, Brucellosis, murine typhus, chronic liver, renal failure, sample that were lysed or icteric and/or turbid were excluded from the study.

Sample and Clinical Data Collection: Following the written informed consent by patients, ~10 mL of venous blood was collected by trained laboratory staff at central research laboratory PIMS, into three separate sample aliquots for serological test (IgM ELISA for ST), biochemical parameters, and hematological tests. Blood specimens were collected in a plain tube, gel tube, and Ethylene diamine tetra acetic acid (EDTA) tube for serological, biochemical, and hematological investigations, respectively. Blood for serological and biochemical investigations was allowed to clot and centrifuged at 5000 rpm for 5 minutes to separate the serum. The serum specimen was then stored at -20℃ until further processing. Clinical and demographic characteristics including residence, occupation, clinical course of illness, and travel history were recorded by using a structured questionnaire form. Physical examination findings such as organomegaly, presence of eschar were recorded under the supervision of a physician of the medicine department.

Scrub Typhus Detection by IgM ELISA: The Scrub Typhus Detect ELISA system is designed to detect IgM antibodies specific to O. tsutsugamushi in serum samples. It utilizes an ELISA format with wells coated in recombinant antigens from O. tsutsugamushi (by manufacturer instruction, J-Mitra diagnostics). Serum samples are diluted and added to the wells, allowing IgM antibodies to bind to the antigens. After washing away unbound components, secondary antibodies linked to horseradish peroxidase (HRP) are added, binding to IgM antibodies. A substrate solution with Tetramethyl benzidine (TMB) causes a color change catalyzed by HRP. Stopping the reaction with an acidic solution allows measuring absorbance at 450nm, directly correlating to IgM antibody concentration against O. tsutsugamushi. An optical density (OD) >0.5 was considered positive.

Sample Processing for Biochemical Parameters: Separated serum was used to investigate the biochemical parameters i.e. liver enzymes (serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT)), bilirubin, urea and creatinine level. The investigation was performed by using an automated system (Erba XL 350, Erba. Mannheim, UK). The reference range for different hematological and biochemical parameters was used as suggested by the manufacturers company.

Hematological Parameters: WBC (White Blood Corpuscle) counting was performed as total leucocytes count (TLC), i.e., total leucocytes present per mm3 of blood. WBC count was performed by Erba Elite 580, and Erba 360 automated analyzer (Erba). Erythrocyte sedimentation rate (ESR) was tested by roller 20, cohuyog (Stago) by automated analyzer.

Data Analysis

Data obtained during the study were maintained daily in Microsoft Excel 2016 before statistical analysis and it was later exported to the SPSS for Windows Version 24.0 for further statistical analysis. Frequency distribution and the correlation between different variables (c2-test) were analyzed and calculated using SPSS. A p-value of <0.05 was considered statistically significant.

Ethical Statement

The study was approved by the Institutional ethics committee of PIMS, Udaipur (Reg. No. STU/IEC/2022/95). Written informed consent was taken prior to the collection of blood samples from each patient.

Result and observations

Geographic and Demographic distribution of patients

It was observed in the present study that of 350 confirmed cases of scrub typhus, female patients were dominated than males. Male patients constituted in number of 155 (44.29%) and females were 195 (55.71%) (**Figure 1**). The average mean age of male patients were 41.4 years and females were 41.44 years.

The highest number of patients were seen in the age group of between 41 – 50 years 103 patients (29.42%), this was followed by age group of 31 – 40 years with patients of 95 (27.14%), 21 – 30 years 41 patients (11.71%), 51 – 60 years and 61 – 70 years each had 32 patients (9.14%), in the age groups of 11 – 20 years 19 patients (5.42%), in the age group of >70 years 16 patients (4.57%) and lesser number of patients were seen in the age group of <10 years, only 12 patients (3.42%) **Figure 2**. According to geographical distribution rural population were highest in number 154 (44%). Trial population were 147 in number (42%), followed by urban 49 in number (14%).

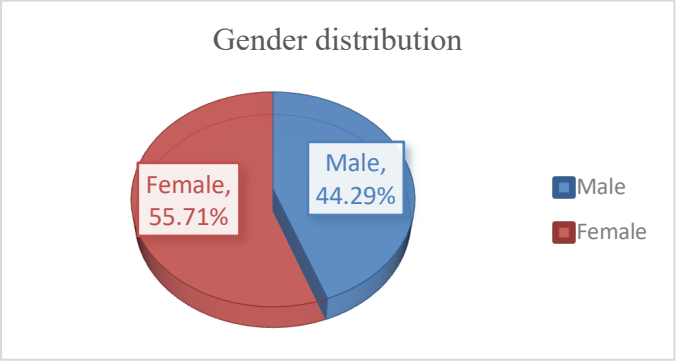

Figure 1: Demographic profile (n=350)

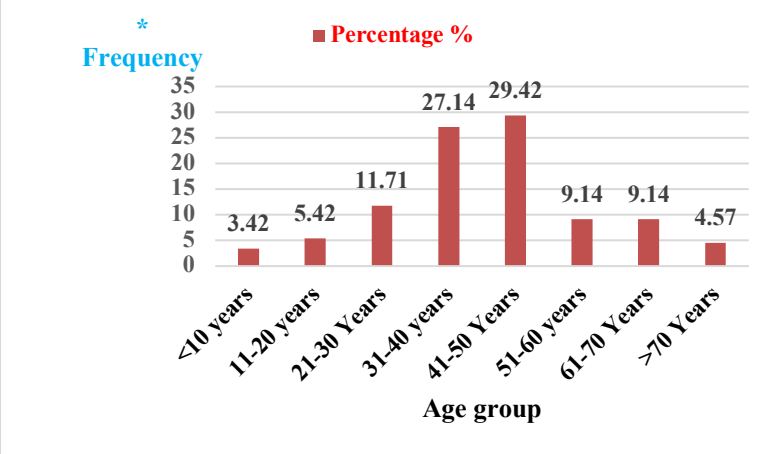

Figure 2: Distribution of study population by age (n=350)

Biochemical and hematological findings of ST patients.

WBC count was low in 5 (1.42%) and raised in 104 (29.71%) patients, decreased platelet count was observed in 129 (36.85%) patients (Table 1), and thrombocytopenia was significantly associated with ST (p-value <0.01). Erythrocyte sedimentation rate (ESR) was raised in 168 (48%) patients. Serum glutamic pyruvic transaminase (SGPT), and serum glutamic oxaloacetic transaminase (SGOT) levels were found to be higher than the normal range in 116 (33.14%), and 112 (32%) ST patients, respectively.

Raised SGPT, on the other hand, was significantly associated with ST (p-value < 0.01) The levels of total bilirubin (BT), direct bilirubin (BD), blood urea, and serum creatinine were high in 51 (14.57%), 68 (19.42%), 87 (24.85%) and 89 (25.42%) respectively (**Table 1, Figure 3**).

Table 1: Biochemical and hematological parameters in ST patients (n=350)

Parameters		No. of patients (n=350)	%
WBCs Counts	Low	5	1.42%
	High	104	29.71%
Thrombocytopenia		129	36.85%
Raised SGOT		112	32%
Raised SGPT		116	33.14%
Raised BT		51	14.57%
Raised BD		68	19.42%
Raised Urea		87	24.85%
Raised Serum creatinine		89	25.42%
Raised ESR		168	36.85%

WBC: White blood corpuscles, ESR: erythrocyte sedimentation rate, SGPT: Serum Glutamic Pyruvic Transaminase, SGOT: Serum Glutamic Oxaloacetic Transaminase, BT: Total bilirubin, BD: Direct bilirubin, * see Supplementary Materials for reference range.

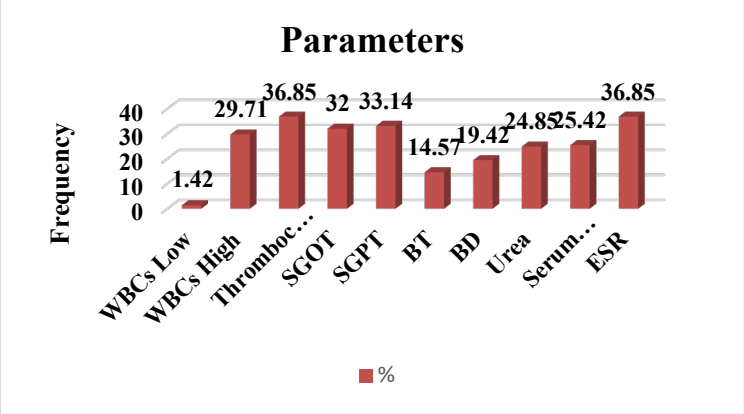

Figure 3: Biochemical and hematological parameters

3.3 Clinical features of scrub typhus patients

Among the 350 ST patients, apart from fever (100%), the most common clinical symptoms were headache (88.57%), myalgia (98%), rashes (75.14%), breathing difficulty (63.14%), vomiting (17.14%), diarrhea (15.14%), and conjunctival suffusion (10.57%). The mean duration of fever was 9± 1 days (**Table 2**). The duration of fever in the majority of the patients (39.71 %, n = 139) was between 5–9 days. Hepatomegaly was recorded in 144 (41.14%) of the patients, splenomegaly was in 145 (41.42%) patients, and lymphadenopathy was noted in 29.71% of the study population. The pathognomonic eschar was present in 83 (23.71%) of the patients (**Table 2**).

Table 2: Sign and symptoms of ST patients (n=350)

Presented sign and symptoms	No. of patients (n=350)	%
Fever with chills	350	100%
Rashes	263	75.14%
Lymphadenopathy	104	29.71%
Vomiting	60	17.14%

Headache	310	88.57%
Myalgia	343	98%
Shortness of breath	221	63.14%
Diarrhea	53	15.14%
Conjunctival suffusion	37	10.57%
Eschar	83	23.71%
Splenomegaly	144	41.42%
Hepatomegaly	145	41.14%

Discussion

Scrub typhus is a significant infectious disease that often goes unnoticed, yet it's considered among the most common emerging and re-emerging diseases globally. The disease poses a substantial risk to a large population, with an estimated one billion people at risk worldwide and approximately one million cases of scrub typhus reported annually. Certain regions of India are witnessing a resurgence of scrub typhus, with reports indicating that it accounts for up to 50% of cases of undifferentiated fever seen in hospitals. In endemic countries, the mortality rate from scrub typhus can be quite high, ranging from 30% to 45% in cases where prompt diagnosis and treatment are not initiated promptly.

In our present study, male patients constituted in number of 155 (44.29%) and females were 195 (55.71%). The average median age of the patients were 41.48 years. **Varghese** et al. reported that the median age of scrub typhus patients in the Southern part of India was 36.5 years, indicating a relatively younger age profile among those affected by the disease. [18]

The highest number of patients were seen in the age group of between 41 – 50 years 103 patients (29.42%), this was followed by age group of 31 – 40 years with patients of 95 (27.14%). Sharma et al.'s study supported this finding, noting that the age group with the highest incidence of scrub typhus was between 30 and 40 years, particularly among females. [19] The increased incidence in females could be linked to their active involvement in agricultural or horticultural activities. Additionally, females often work bare-handed in fields or while cutting grass, increasing their exposure to infected mites inhabiting the soil and scrub vegetation, thus raising their risk of contracting the disease. Fever was present in all the patients (100%) and mean febrile duration of fever was about 9± 1days before attending the hospital. Headache was observed in 88.57%, myalgia 98%, vomiting in 17.14% of the patients.

Tsay et al.'s study yielded almost identical results, showing similar findings to the previous study. Specifically, around 7% of patients exhibited altered sensorium, with a Glasgow Coma Scale (GCS) score of less than 15 in 6.8% of cases upon admission. In contrast, Griffith et al.'s study reported a higher rate of altered mental status with a GCS score of less than 15 in 30% of patients upon admission. [20-21]

Leucocytosis was observed in 29.71% of cases, while leukopenia was noted in 1.42% of cases. Additionally, thrombocytopenia was present in 36.85% of the patients studied. Similar findings by Vikrant et al. discovered leucocytosis in 44.3% of patients. They also observed thrombocytopenia in 61.5% of the individuals included in their research. [22]

In this study, 10.57% of scrub typhus (ST) patients exhibited redness in the eye, suggesting potential ocular involvement. Approximately one-third of all ST patients presented with rashes (75.14%). Eschar was observed in 23.71% of the patients. The prevalence of rashes (ranging from 6% to 93%) and eschar (ranging from 3% to 90%) has been reported to vary among ST patients across endemic regions worldwide. The presence of the characteristic eschar varies depending on the geographical region and the capacity of O. tsutsugamushi strains to induce eschars. [23,24,25]

It's worth noting that indigenous individuals living in endemic areas often experience less severe illness related to scrub typhus, and they may not exhibit any rash or eschar. While the presence of an eschar can be a specific diagnostic indicator, its painless nature and location on the body, primarily on the trunk, inguinal, genital, and axillary areas, might not draw immediate attention from both patients and clinicians. This reluctance to show eschars on intimate body parts to healthcare providers may have contributed to the lower observed prevalence of eschars in our study. [26]

In the present study, 29.71% of our patients had lymphadenopathy. A wide range (22%–53%) of lymphadenopathy also has been reported in different studies. [27,28,29], and some have suggested that the presence of generalized lymphadenopathy suggests a late presentation and a worse outcome. [30]

In present study diarrhea was observed in 15.14% of the patients. A study conducted in Sri Lanka in 2013 reported a low incidence of diarrhea, with only 5% of cases exhibiting this symptom. [26]

In contrast to these findings, other studies conducted elsewhere have reported a higher

prevalence of diarrhea among scrub typhus patients. [20,31,32]

As evidenced by our study, elevated levels of liver enzymes such as SGPT (33.14%), and SGOT (32%) and raised level of blood urea (24.85%), serum creatinine (25.42%) are commonly observed manifestations of scrub typhus (ST). In ST patients, elevated SGOT levels have been reported in 78% to 89% of cases, elevated SGPT levels in 64% to 92%, and elevated alkaline phosphatase (ALP) levels in 27% to 84% of cases. [33]

In present study, we observed that 41.14% of patients exhibited hepatomegaly, while 41.42% of patients had splenomegaly. According to Vivek Kumar et al.'s study, hepatomegaly was observed in 69% of patients, indicating a significant proportion of individuals with enlarged livers. In contrast, splenomegaly was noted in 41% of cases. Additionally, eschar was observed in nine cases, further adding to the spectrum of clinical manifestations associated with the disease.

Hepatomegaly and splenomegaly in scrub typhus result from the bacterium causing widespread inflammation and damage to cells in organs like the liver and spleen. This inflammation leads to increased vascular permeability and immune cell accumulation, with direct invasion of these organs further contributing to their enlargement. Overall, these processes are common causes of hepatomegaly and splenomegaly in scrub typhus patients.

The primary strength of our study lies in the inclusion of confirmed cases of scrub typhus, as evidenced by the presence of IgM antibodies against O. tsutsugamushi. These selection criteria ensure a more accurate and reliable identification of patients with the disease, enhancing the validity and robustness of our findings.

Diagnosing scrub typhus in India is complex due to varied symptoms, often no eschar, and scarce specific tests. In such settings, we suggest relying on strong suspicion, detailed assessments, and empirical antibiotic treatment for febrile patients with multi-organ involvement.

Conclusion

This study underscores the significant prevalence of scrub typhus, urging clinicians to prioritize it as a potential cause of acute febrile illness. Females and travelers are particularly susceptible, necessitating thorough examinations in high-risk areas. Future studies should focus on establishing baseline antibody prevalence, identifying circulating genotypes, and understanding disease persistence from recent infections. These efforts are crucial for improving the diagnosis and management of scrub typhus infections, especially in regions like Rajasthan.

Abbreviations

ST – Scrub Typhus

BD - Direct bilirubin

BT - Total bilirubin

LMIC - Low-and middle-income country

PCR - Polymerase chain reaction

ELISA - Enzyme linked immunosorbent assay

SGOT - Serum glutamic oxaloacetic transaminase

SGPT - Serum glutamic pyruvic transaminase

TLC - Total leukocyte count

UFI - Undifferentiated febrile illness

PLT – Platelet Counts

WBCs – White blood corpuscle

ESR – Erythrocyte sedimentation rate

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