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A retrospective observational study analyzing the demographic profile, clinical presentations, and complications of scrub typhus in a tertiary health-care center

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ABSTRACT

Background: Scrub typhus is an acute febrile illness caused by an obligate intracellular, rickettsial organism, *Orientia tsutsugamushi*. Around one million cases are reported annually, mostly from the region of the Tsutsugamushi triangle. In India, scrub typhus has been reported from various states. **Aims and Objectives:** This study was done to analyze the demographic data, clinical presentations, and complications of scrub typhus in our setting. **Materials and Methods:** A retrospective observational study was done on 65 patients who were admitted to a tertiary health-care center in South India from January 2018 to January 2024 with acute febrile illness and who were diagnosed to have scrub typhus by either scrub typhus immunoglobulin M antibody detection by enzyme-linked immunosorbent assay or Weil Felix OX-K titers >1:160. Demographic data, clinical presentations, treatment details, complications, and outcomes were studied. **Results:** The most common presenting complaint was fever (96.9%), followed by myalgia (72.3%), headache (55.4%), and vomiting (47.7%). Transaminitis was seen in 55.4% of the patients, thrombocytopenia in 44.61%, and severe thrombocytopenia in 7.6% of the patients. Other complications seen were acute kidney injury (29.2%), pneumonia (29.2%), acute respiratory distress syndrome (ARDS) (10.8%), and meningoencephalitis (7.69%). The majority of our patients (27%) were from the Western Ghat region. **Conclusion:** Scrub typhus is a serious acute infection that may progress to multiorgan dysfunction and lead to mortality if not treated early. Intensive care requirements and longer hospital stays were higher in patients with central nervous system involvement, ARDS, and those requiring dialysis. A high index of clinical suspicion and prompt treatment are paramount to improve patient outcomes.

Key words: Scrub typhus; *Orientia tsutsugamushi*; eschar

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INTRODUCTION

Scrub typhus, also called Tsutsugamushi disease or bush typhus, is an acute febrile illness caused by the obligate intracellular, Gram-negative, rickettsial organism named *Orientia tsutsugamushi*. It is transmitted by the bite of the larva of trombiculid mite (chiggers).[1]

It is one of the re-emerging, tropical diseases which pose a diagnostic dilemma to many clinicians mainly due to its varied symptomatology. It also has a similar presentation to other acute febrile illnesses such as dengue, malaria, and leptospirosis. In South-eastern Asia, it is thought that up to one million cases occur per year, and a significant proportion of hospital admissions for acute undifferentiated fever have been shown to be attributable to scrub typhus.[2]

The majority of the cases have been reported annually from the Tsutsugamushi triangle, an endemic zone of scrub

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typhus consisting of Japan, China, Taiwan, South Korea, Indonesia, Thailand, Sri Lanka, Nepal, India, northern Pakistan, Papua New Guinea, and the Australian states of Queensland, and northern New South Wales (Figure 1).[3,4]

This disease has been known to be endemic to India since the time of the Second World War. Scrub typhus has been reported from the following states: Haryana, Jammu, and Kashmir, Himachal Pradesh, Uttaranchal, West Bengal, Assam, Maharashtra, Kerala, and Tamil Nadu.[5]

In certain parts of India, scrub typhus accounts for almost 30–50% of cases of pyrexia of unknown origin, requiring hospitalization.[6,7] One-third of the cases of scrub typhus requiring hospitalisation[8] progress to multiorgan dysfunction syndrome (MODS) with involvement of the renal, hepatic, neurological, respiratory, and cardiovascular systems leading to high mortality rates.[9] The case fatality rate of scrub typhus varies between 1.3% and 33.5%, depending upon the organ system involved and the development of MODS.[10-12]

Acute onset fever is the most common presenting symptom of scrub typhus. Other symptoms include cough, headache, myalgia, breathlessness, nausea, and vomiting.[13] In around 10–90% of the people, an eschar may be found on thorough examination (common sites being axilla, groin, abdomen, and back); however, this may be variable.[14] The infection may vary from a self-limiting illness to a life-threatening infection with MODS and death. The majority of the complications include acute kidney injury, meningoencephalitis, acute respiratory distress syndrome (ARDS), and myocarditis, all of which play a major role in the prognosis of the patient. The diagnosis is made based on the Weil Felix test, which is non-specific, or the gold standard scrub typhus immunoglobulin M (IgM) antibody detection by enzyme-linked immunosorbent assay (ELISA) or immunofluorescence.

Given the varied clinical presentation, the possibility of multiorgan dysfunction, and the high case fatality rates, scrub typhus poses a significant clinical challenge and has re-emerged as one of the more serious tropical infections. Given the lack of substantial data from coastal India and the rising incidence of this infection, there still remains a gap in our knowledge regarding the disease.

Aims and objectives

The objective of this study was to analyse the epidemiology, various clinical presentations, complications and outcomes of scrub typhus, thereby helping the clinician make an early diagnosis and navigate treatment challenges.

MATERIALS AND METHODS

The approval was obtained from Father Muller Institutional Ethics Committee under the letter reference number (FMIEC/CCM/708/2024) dated August 13, 2024. This was a retrospective observational study done on patients who were admitted to the Department of Medicine in Father Muller Medical College, Mangalore, from January 2018 to January 2024. Electronic case records of 65 patients were reviewed. Demographic data, clinical presentations, treatment details, complications, and outcomes were studied and analyzed.

Inclusion criteria

Patients with acute febrile illness, aged >18 years and who were positive for scrub typhus IgM antibody through ELISA technique and/or having Weil Felix OX-K titers >1:160, were included in the study.

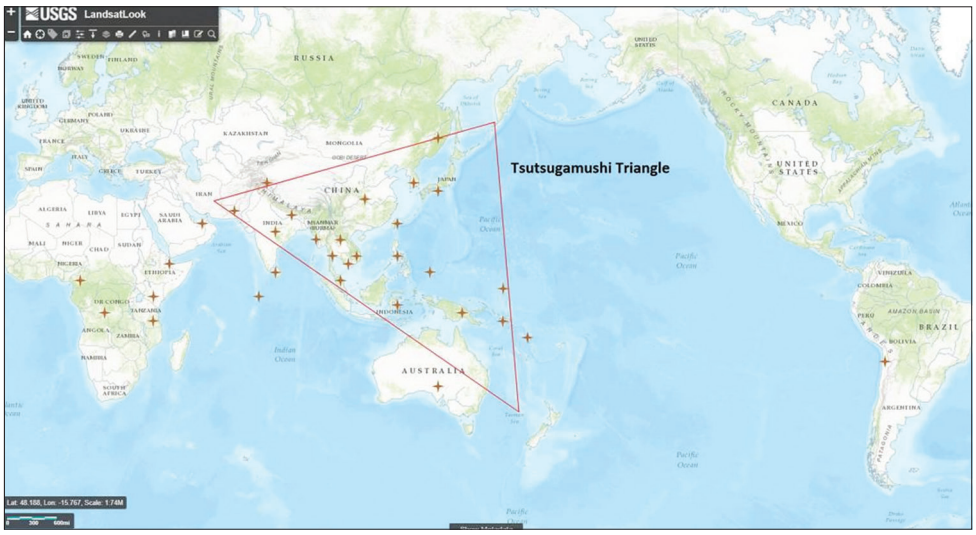

Figure 1: Area distribution of Tsutsugamushi triangle

Exclusion criteria

Patients with other coexistent acute febrile illnesses such as dengue, leptospirosis, and malaria were excluded. Categorical data were summarized using frequency and percentages. Quantitative normal data were summarized by mean and standard deviation, and quantitative non-normal data were summarized by median and interquartile range. The comparison was ascertained by the Chi-square test. Analysis was performed using the Statistical Packages for the Social Sciences 23 software, and the level of significance was 0.05.

RESULTS

Patient characteristics

The mean age of participants was 48.338 years. The majority of the study participants were males (n-37, 56.9%), followed by females (n-28, 43.1%). The majority of the study participants belonged to the age group of more than 50 years (49.2%). Twenty-one patients were in the age group of 30–50 years (32.3%), and 12 patients were in the age group of 17–30 years. Diabetes was coexisting comorbidity in 19 patients (29.2%), hypertension in 14 patients (21.5%), and chronic kidney disease in 2 patients (3.1%). Some patients had more than one comorbidity.

Demographic characteristics

A large proportion of the patients (27%) were from the Western Ghat region, followed by Kasargod (20%), Mangalore (13%), and Kannur (9%).

Clinical profile

Fever was the most common presenting complaint, seen in 63 of the 65 participants (96.9%). This was followed by myalgia (72.3%), headache (55.4%), vomiting (47.7%), cough (36.9%), and abdominal pain (30.8%). Four participants also presented with seizures (6.2%). The mean duration of fever was 7 days.

Complications

The most common biochemical abnormality was transaminitis, which was seen in 36 patients (55.4%). Thrombocytopenia was seen in 29 patients (44.61%), and severe thrombocytopenia (platelet count <50,000 cells/μL) was seen in 5 patients (7.6%). Acute kidney injury (AKI) was seen in 29.2% of the patients. Hemodialysis was required in 9.2% of the patients. Pneumonia was seen in 29.2% of the study population, and among these, 10.8% of patients developed ARDS, and 4.6% of them required mechanical ventilation. Five patients (7.69%) were confirmed to have meningoencephalitis, and this was established after cerebrospinal fluid examination. Twenty-eight patients (38.4%) had two or more organ dysfunction. Intensive care management was required in 26.2% of the study population.

The need for intensive care unit (ICU) admission and prolonged hospital stay was seen to be statistically significant in patients with meningoencephalitis, ARDS, and those who required dialysis.

There was no significant association that was found between the presence of diabetes and the development of complications.

Treatment

The study population was treated with doxycycline (n=63) in combination with ceftriaxone (n=42) or piperacillin–tazobactam (n=19) or meropenem. All 65 participants improved and were discharged once stable.

DISCUSSION

Scrub typhus affects about one million people across the globe every year[15] and is a potentially fatal infection if not treated earlier.

Our study consisted of 65 patients, out of which the majority were males 37 patients (56.9%), and the majority of the study participants belonged to the age group of more than 50 years (49.2%). In a study done by Shrestha et al.,[16] in Nepal, it was seen that out of 40 seropositive cases, 28 (70%) were female patients, and the majority of patients were in the age group of 30–60 years (47.5%). Another study conducted by Thapa et al.,[17] in Chitwan, Nepal, showed an increased prevalence of cases among females (314 out of 524 patients) as compared to males and showed a statistically significant association of scrub typhus cases with gender of the patients (P<0.001), and the occurrence of scrub typhus was more common among age group of 51–60 years (37.2%) which was also statistically significant (P<0.003). However, studies by Varghese et al.,[8] Sharma et al.,[9] Narvencar et al.,[10] and Medhi et al.,[18] reported no significant association of scrub typhus cases with the age and gender of the patient (P>0.05). The higher preponderance of cases in males in our study may be attributed to increased outdoor or farming activity, resulting in increased exposure to the mites.

The most common symptom that patients presented with was fever (96.9%), followed by myalgia (72.3%), headache (55.4%), vomiting (47.7%), cough (36.9%), abdominal pain (30.8%), and seizures (6.2%) (Table 1). In a study done by Varghese et al.,[8] in Vellore, Tamil Nadu, the most common clinical manifestation was fever (100%) followed by nausea/vomiting (54%), shortness of breath (49%),

Table 1: Clinical presentations, complications, and outcomes

Parameter studied	Frequency	Percentage
Chief complaints		
Fever	63	96.9
Myalgia	47	72.3
Headache	36	55.4
Vomiting	31	47.7
Cough	24	36.9
Abdominal pain	20	30.8
Seizures	4	6.2
Complications		
Transaminitis	36	55.4
Thrombocytopenia	29	44.61
AKI	19	29.2
Pneumonia	19	29.2
Meningoencephalitis	5	7.69
ARDS	7	10.8
Dialysis	6	9.2
Outcome		
ICU admission	17	26.2
Ventilator requirement	3	4.6
Recovered	65	100.0

AKI: Acute kidney injury, ARDS: Acute respiratory distress syndrome, ICU: Intensive care unit

headache (46%), and altered sensorium (26%). A study done by Sharma et al.,[9] in Chandigarh noted that the most common presenting complaint was fever (85%) followed by breathlessness (42%), jaundice (32%), abdominal pain (28%), and seizure (7%). A study done by Thapa et al.,[17] in Chitwan, Nepal, also found that the most common symptom was fever (100%), followed by anorexia (64.7%), headache (54.6%), and seizures (6.1%). A study done by Griffith et al.,[19] in Vellore, Tamil Nadu, found that fever was seen in 100% of patients, breathlessness in 68.5%, and altered sensorium in 25.2%. A study done by Mahajan et al.,[20] in Himachal Pradesh, also noted that the most common symptom was fever (100%), followed by vomiting (42.8%), myalgia (38%), and headache (38%).

Eschar is considered a pathognomic sign of scrub typhus; however, the presence of eschar was not found in any patients in our study. In a study done by Varghese et al.,[8] in Vellore, Tamil Nadu, eschar was seen in a significant number of the population that is 43.5%; also Griffith et al.,[19] in Vellore, Tamil Nadu, found eschar in 47 patients (41.6%), Shrestha et al.,[16] in Nepal, it was seen that out of 40 seropositive cases, eschar was seen in 11 (27.5%) cases and Sharma et al.,[9] in Chandigarh found eschar in 32 patients (14%), Narvencar et al.,[10] in Goa eschar was seen only in 2 patients (13.3%). However, a study done by Mahajan et al.,[20] in Himachal Pradesh found that eschar was seen only in 2 patients (9.5%), Thapa et al.,[17] in Chitwan, Nepal found eschar in 6.5% of cases, and Medhi et al.,[18] in Assam, it was seen only in 2 patients (1.61%). The variation in the occurrence of eschar is probably related to the varied strains of the organism, immunity, and its geographic distribution.[9]

In our study, the complications noted were transaminitis (55.4%) followed by thrombocytopenia (44.61%), AKI (29.2%) and pneumonia (29.2%), ARDS was seen in 7 patients (10.8%), dialysis requirement in 6 patients (9.2%), and meningoencephalitis was seen in 5 patients (7.69%) (Table 1). A study done by Sharma et al.,[9] which showed thrombocytopenia in 90%, transaminitis in 61%, AKI in 32%, and ARDS in 25% of the patients. A study done by Thapa et al. [17] found thrombocytopenia in 73.7%, raised AST in 76.1%, and raised alt in 70%. A study done by Griffith et al.,[19] found thrombocytopenia in 86%, ARDS in 73.3%, and dialysis requirement in 13 patients (11.2%). Mahajan et al.[20] noted transaminitis in 66.7%, AKI in 66.7%, seizures in 19%, and ARDS in 9.5%. Narvencar et al.[10] noted that transaminitis was seen in 80%, ARDS (60%), thrombocytopenia (40%), AKI in 33%, and meningitis in 6.7%. Most studies have shown the estimated incidence rates of scrub typhus meningoencephalitis to be between 9% and 23.3%.[20-22]

In our study, 28 patients (38.4%) had two or more organ dysfunction. Intensive care management was required in 17 patients (26.2%) of the study population, and three patients required ventilatory support (4.6%) (Table 1). In a study done by Griffith et al.,[19] MODS was seen in 104 out of 107 patients, and 74 patients (63.8%) required invasive ventilation. In a study by Narvencar et al.,[10] MODS was seen in 5 patients (33.3%), Varghese et al.[8] was 34%, and Sharma et al.[9] was 20%.

In our study, all patients were treated with doxycycline. Those having meningoencephalitis were treated with injectable doxycycline instead of the conventional oral dosing. This may have contributed to better patient outcomes, as oral doxycycline does not cross the blood–brain barrier beyond 15–20%.

The need for ICU admission was higher in patients who had AKI, pneumonia, ARDS, and meningoencephalitis ($P<0.05$) (Table 2). However, the presence of comorbidities such as diabetes mellitus was not associated with increased complications and ICU admission (Table 3).

The case fatality of scrub typhus has been estimated to be between 7 and 30%.[23] However, there was no mortality seen in our study. In a study done by Griffith et al.,[19] mortality was seen in 28 patients (24.1%), Narvencar et al.[10] had a mortality of 5 patients (33.5%), Mahajan et al.[20] had a mortality of 14.2%, Varghese et al.[8] was 9%, and Sharma et al.[9] had a case fatality rate of 43% with MODS and 11% without MODS. The mortality of patients with

Table 2: Association of complications with need for ICU stay

Complications	ICU stay		Test statistic	P-value
	Yes (n=17)	No (n=48)		
Transaminitis				
Yes	10 (15.4)	26 (40.0)	0.110	0.740
No	7 (15.4)	22 (33.8)		
AKI				
Yes	10 (15.4)	9 (13.8)	9.746	0.002
No	7 (10.8)	39 (60.0)		
Pneumonia				
Yes	9 (13.8)	10 (15.4)	6.256	0.012
No	8 (12.3)	38 (58.5)		
Meningoencephalitis				
Yes	5 (7.7)	0	15.294	0.0001
No	12 (18.5)	48 (73.8)		
ARDS				
Yes	6 (9.2)	1 (1.5)	14.409	0.0001
No	11 (16.9)	47 (72.3)		
Dialysis requirement				
Yes	5 (7.7)	1 (1.5)	11.190	0.0001
No	12 (18.5)	47 (72.3)		

AKI: Acute kidney injury, ARDS: Acute respiratory distress syndrome, ICU: Intensive care unit

Table 3: Association of the presence of diabetes and development of complications

Complications	Diabetes		Test statistic	P-value
	Yes (n=19)	No (n=46)		
Transaminitis				
Yes	10 (15.4)	26 (40.0)	0.082	0.774
No	9 (13.8)	20 (30.8)		
AKI				
Yes	6 (9.2)	13 (20.0)	0.072	0.789
No	13 (20.0)	33 (50.8)		
Pneumonia				
Yes	5 (7.7)	14 (21.5)	0.110	0.740
No	14 (21.5)	32 (49.2)		
Meningoencephalitis				
Yes	1 (1.5)	4 (6.2)	0.223	0.637
No	18 (27.7)	42 (64.6)		
ARDS				
Yes	1 (1.5)	6 (9.2)	0.847	0.357
No	18 (27.7)	40 (61.5)		
Dialysis				
Yes	4(6.2)	2(3.1)	4.478	0.034
No	15 (23.1)	44 (67.7)		

AKI: Acute kidney injury, ARDS: Acute respiratory distress syndrome, ICU: Intensive care unit

scrub typhus is dependent on the circulatory load of *O. tsutsugamushi*. The other factors contributing to mortality include the time of presentation and the delay in initiation of appropriate antibiotic therapy. In our study, the mean duration of presentation to the hospital following the onset of symptoms was 7 days. The presence of complications such as ARDS, renal failure, hepatic dysfunction, and meningoencephalitis have been proven to be independent predictors of mortality.[8] The improved outcomes in our study may be attributed to the early presentation to the hospital and early initiation of therapy.

Limitations of the study

This was a retrospective observational study that was conducted in a single medical center. More number of study patients would help in further analysis of various parameters.

CONCLUSION

Scrub typhus is a serious acute infection, which may progress to multiorgan dysfunction and lead to mortality if treatment is not commenced early. Scrub typhus is endemic to places that are also affected by diseases such as dengue, malaria, and leptospirosis. The geographical distribution of the majority of our patients were from the Western Ghat region. Hence, a high index of clinical suspicion, prompt investigation, and early initiation of treatment are paramount to improve patient outcomes. Scrub typhus should also be considered a differential diagnosis in patients with acute febrile illness. The need for intensive care treatment and longer hospital stays was seen to be statistically significant in patients with meningoencephalitis, ARDS, and those who required dialysis. Increasing awareness of this disease among clinicians in endemic regions, availability of rapid diagnostic tests, and early treatment have to be prioritized.

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LAM- Definition of intellectual content, literature survey, prepared the first draft of the manuscript, implementation of the study protocol, data collection, data analysis, and manuscript preparation; **SM-** Literature survey, input on concept and design of the study, coordination and manuscript preparation, editing and revision, and submission of the article; **AJ-** Editing and revision of the manuscript.

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