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Clinico-demographic profile of scrub typhus: A prospective study

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Abstract
Background and Objectives: Scrub typhus, an acute febrile illness caused by *Orientia tsutsugamushi*, is endemic in many parts of India including Rajasthan. We aim to study the clinico-demographical profile of scrub typhus and to identify the markers which may help in early diagnosis and predicting the severity of disease.
Methods: A prospective study was conducted at Government Medical College, Kota including 100 IgM ELISA confirmed scrub typhus patients getting admitted between September 2019 and September 2020.
Results: The mean age of 100 patients (60 females and 40 males) is 41.13±15.78 years. Farmers (65%) are mostly affected specially from rural areas (85%). Manifestations include fever (100%), myalgia (68%), headache (56%), breathlessness (48%), abdominal pain (48%), cough (46%), vomiting (41%), diarrhea (9%), altered sensorium (9%), convulsions (2%), hepatomegaly (64%), splenomegaly (36%), jaundice (34%), eschar (12%), lymphadenopathy (8%) and rashes (5%). 72% developed complications, such as hepatic dysfunction (52%), ARDS (32%), acute kidney injury (36%), multiple organ dysfunction (35%), encephalitis (7%), shock (7%), myocarditis (4%) and epididymo-orchitis (1%). Leucocytosis (p=0.009), thrombocytopenia (p=0.040), hypoalbuminemia (p=0.037), raised LDH (p=0.001) and hypertriglyceridemia (p=0.001) are significantly associated with complications. Mean length of hospital stay is 5.6 days with a mortality rate of 2%.
Conclusion: Scrub typhus should be considered in the differential diagnosis of acute febrile illness associated with hepatosplenomegaly, thrombocytopenia, elevated liver enzymes, hypertriglyceridemia, renal dysfunction or ARDS, with or without the presence of eschar. A high index of suspicion is required for early diagnosis and treatment to prevent morbidity and mortality.

Keywords: eschar, *Orientia tsutsugamushi*, scrub typhus

Introduction
Scrub typhus is an acute febrile illness caused by *Orientia tsutsugamushi*, gram negative intracellular bacteria, which is accidentally transmitted to humans by the bite of larval stage of trombiculid mite [1]. The clinical spectrum of scrub typhus varies from mild to severe form. Fever is the most common manifestation, accompanied by headache, myalgia and cough. Incubation period varies from 7-21 days. The bite of trombiculid mite shows a characteristic black eschar resembling a cigarette burn which is useful for making the diagnosis. Complications include interstitial pneumonia/ARDS, acute renal injury, hepatic dysfunction, circulatory collapse and encephalopathy [2]. A late presentation, delay in diagnosis and treatment, and varying levels of antibiotic resistance exhibited by the organism are factors responsible for high mortality [3].
Scrub typhus is endemic in many parts of India including Rajasthan. Due to lack of awareness, low index of suspicion among clinicians and clinical symptoms mimicking other etiologies of acute febrile illness like dengue, malaria and typhoid, it remains under diagnosed which leads to high morbidity and mortality. It is necessary to identify the diagnostic markers and determine the predictors of severe disease in order to reduce the mortality due to the delay in diagnosis/treatment and the high incidence of complications. This study was carried out with an aim to study the clinical and demographical profile of scrub typhus and to identify the markers which may help in early diagnosis and predicting the severity of disease.

Material and Methods
A prospective study was conducted at Government Medical College, Kota between September 2019 and September 2020. 100 scrub typhus patients, confirmed by IgM ELISA method, getting admitted in the hospital, were included in our study irrespective of age and gender. Those who were scrub typhus positive with rapid card test but negative by IgM ELISA or diagnosed to have some other associated infection or having co-morbid conditions like chronic renal failure, chronic liver disease or malignancy were excluded. Detailed history taking, clinical examination and routine investigations such as complete blood count, renal function test, liver function test, lipid profile and serum electrolytes were performed in all patients. X ray chest PA view, ECG, ultra sound abdomen, echocardiography, CT scan brain/MRI brain was done as needed. Treatment regimen specially the type, dose and days of antibiotic given were recorded in each case. Any complication during the hospital stay was noted. The patients were then divided into 2 groups, complicated, with any complication, and uncomplicated, with no complications. The results were analyzed statistically. Continuous variables were summarized as mean and standard deviation and the categorical variables were summarized as proportion or percentages. Chi-square test and independent student t-test were used to compare categorical and continuous variables respectively, between two groups. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 26.0 software. P value <0.05 was considered statistically significant.

Results

Distribution

A total of 100 scrub typhus patients were assessed. The age group of patients ranged from 14 to 80 years with the mean age of 41.13 years and a standard deviation of 15.78 years. The study included 60 females and 40 males. (Table 1) Among 100 patients, there are 65 farmers, 18 students, 15 housewives, 1 shop keeper and 1 laborer by occupation. 85 patients are from rural area and 15 patients from urban area.

Table 1: Age and Sex Distribution of Patients

Age groups (in years)	No. of Males	No. of Females	Total
<20	6	10	16
21-40	14	18	32
41-60	14	27	41
61-80	6	5	11
Total	40	60	100

Clinical Manifestations

All patients presented with fever. The duration of fever ranged from 3 to 20 days with a mean of 8.03 ±3.59 days. Out of the 100 patients, 32 had fever for 5 days or less, 49 had fever for 6-10 days and 19 had fever for more than 10 days before hospitalization. As per the intensity of fever, 9 had low grade fever, 60 had moderate grade fever and 31 had high grade fever. 54 patients demonstrated continuous type fever whereas 46 patients had intermittent type of fever. Other manifestations include myalgia (68%), headache (56%), breathlessness (48%), abdominal pain (48%), cough (46%), vomiting (41%), diarrhea (9%), altered sensorium (9%) and convulsions (2%). Physical Examination revealed hepatomegaly (64%), splenomegaly (36%), icterus (34%), pleural effusion (13%), ascites (13%), eschar (12%), lymphadenopathy (8%) and maculopapular rashes (5%). (Figure 1)

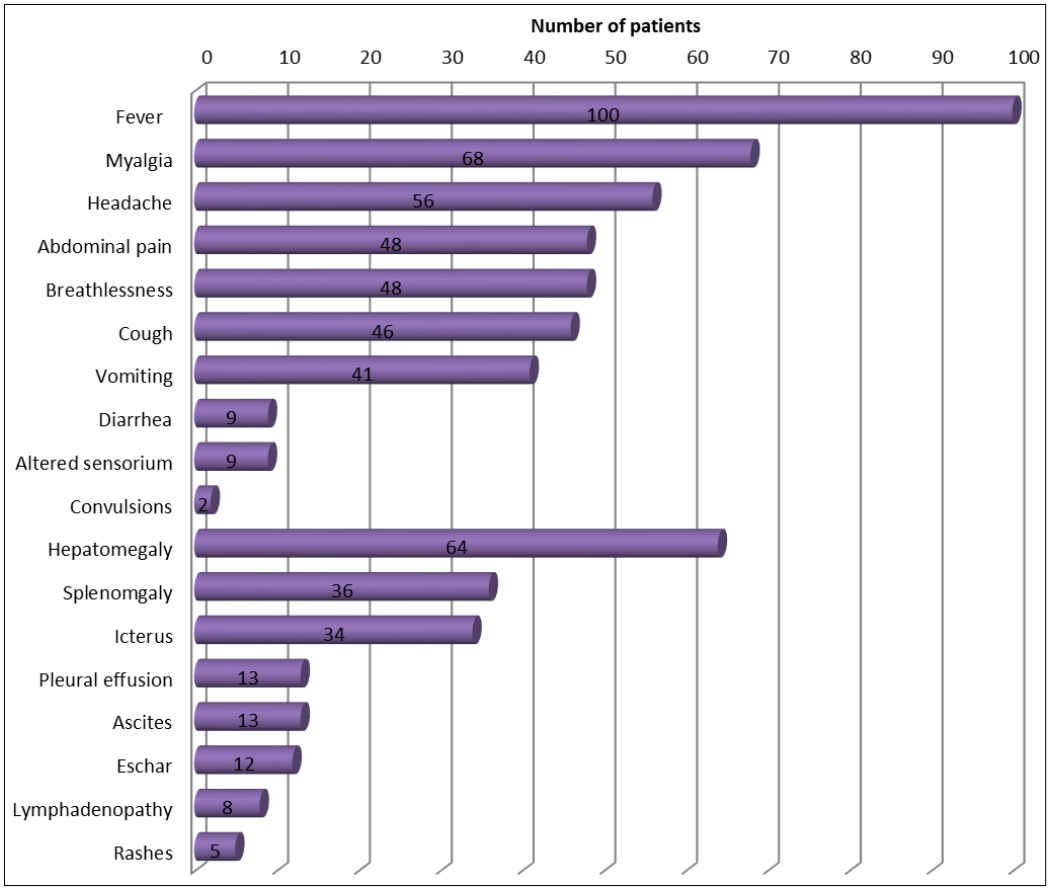

Fig 1: Clinical manifestations of patients

Laboratory profile predominantly revealed hypertriglyceridemia (92%), low hematocrit (80%), thrombocytopenia (77%), anemia (60%), hypoalbuminemia (61%), leucocytosis (31%), neutrophilia (29%) and deranged liver and kidney function tests (Table 2).

Table 2: Abnormal Laboratory Parameters

Laboratory finding	No. of patients
Raised SGOT (>40IU/L)	93
Raised S. triglyceride (>150 mg/dl)	92
Raised LDH (>480IU/L)	89
Low hematocrit (<35%)	80
Raised SGPT (>40IU/L)	80
Thrombocytopenia(platelet count <1.5 lac/uL)	77
Low Albumin (<3gm%)	61
Anemia (Hb<11g/dl)	60
Raised urea (>45mg/dl)	54

Raised total bilirubin (>1.2mg/dl)	50
Raised ALP (>140IU/L)	49
Hyponatremia (<135mmol/L)	45
Hypokalemia (<3.5mmol/L)	39
Raised creatinine (>1.5mg/dl)	32
Leucocytosis (WBC>11000/uL)	31
Neutrophilia (ANC>8000/uL)	29
Lymphopenia (ALC<1000/uL)	19
Lymphocytosis (ALC>4000/uL)	19
Hypoglycem RBS <60mg/dl)	3

ECG showed sinus tachycardia (28%), non-specific ST-T changes (7%), atrial fibrillation (2%) and left bundle branch block (1%). 64 patients were having normal electrocardiographic findings. Chest X-ray revealed bilateral lung opacities (36%), pleural effusion (13%) and cardiomegaly (3%). 48 patients were having normal chest X-ray findings. The average duration of hospital stay for the patients was 5.6 days. 72 patients developed complications, such as hepatic dysfunction (52%), ARDS (32%), acute kidney injury (36%), multiple organ dysfunction (35%), encephalitis (7%), shock (7%), myocarditis (4%) and epididymo-orchitis (1%). 28% had no complication (Figure 2). 18 patients required oxygen support, 2 required non invasive ventilation, 4 required vasopressor support and 2 patients required dialysis.

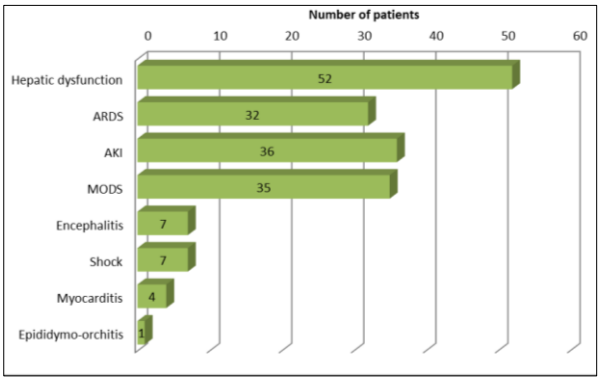

Fig 2: Complications seen in patients

Out of the 100 patients, 83 received azithromycin 500mg OD and doxycycline 100mg BD, and 17 patients received azithromycin 500mg OD and chloramphenicol 500mg QID. In 5 patients, treatment protocol was changed from doxycycline to chloramphenicol as they did not show any response to doxycycline after 3 days. No side effect of drugs was observed in any patient during hospitalization. Out of 100 patients, 97 patients got cured and discharged, 1 patient left against medical advice (LAMA) and 2 patients expired. The clinical and demographic profile of patients who had complications is compared with that of those who did not have any complication. No significant association of complications is seen with age, gender, region, duration of symptoms or the presence of eschar. (Table 3)

Table 3: Comparison between complicated and uncomplicated cases

Age group	Uncomplicated cases	Complicated cases	
<20 years	8	8	
21-40 years	7	25	p = 0.092
41-60 years	12	29	χ^2 = 6.420
>60 years	1	10	
Gender			
Female	19	41	P = 0.317
Male	9	31	χ^2 = 1.000
Region			
Rural	23	62	p = 0.249
Urban	5	10	χ^2 =6.177
Duration of symptoms			
<5 days	13	19	p = 0.154
6-10 days	11	38	χ^2= 3.733
>10 days	4	15	
Eschar			
Present	3	9	p= 0.805
Absent	25	63	χ^2 =0.0609

On comparing laboratory parameters between complicated and uncomplicated cases, mean total leucocyte count of complicated cases (10322±5399 /uL) is significantly higher than that of uncomplicated cases (7651±3777 /uL, p=0.01). The mean hemoglobin (p=0.008), mean platelet count (p=0.01) and mean hematocrit (p=0.000) of complicated cases are significantly lower than that of uncomplicated cases (Table 4). There is significant association of complications with leucocytosis (p=0.009), thrombocytopenia (p=0.040), hypoalbuminemia (p=0.037), raised LDH (p=0.001) and hypertriglyceridemia (p=0.001).

Table 4: Comparison of laboratory parameters between complicated and uncomplicated cases

Parameter	Uncomplicated (n=28)	Complicated (n=72)	P value
Leucocytosis	3	27	0.0086
Thrombocytopenia	18	60	0.038
Hypoalbuminemia	22	67	0.037
Hypertriglyceridemia	21	71	0.00009
Laboratory values (mean±SD)			
Hb (g/dl)	11.12±1.97	9.91±2.06	0.008
TLC (/uL)	7651 ±3777	10322 ±5399	0.01
HCT (%)	32.67 ±5.40	28.41±5.39	0.000
Platelet count (*10^3/uL)	133 ±103	90 ±67	0.01
RBS (mg/dl)	112.8±28.2	103.9±28.7	0.165
S. urea (mg/dl)	28.2±9.99	98.4±83.9	0.000
S. creatinine (mg/dl)	0.95±0.22	2.43±2.36	0.001

Total bilirubin (mg/dl)	0.63±0.41	4.49±4.84	0.000
SGOT (IU/L)	79.96±48.70	225.9±205	0.000
SGPT (IU/L)	65.75±38.59	133.6±143.3	0.015
ALP (IU/L)	130±72.27	217.4±156.1	0.005
S.albumin (g/dl)	3.12±0.40	2.62±0.49	0.000
LDH (IU/L)	694.2±365.8	1390.2±1106.9	0.001
S.triglyceride (mg/dl)	210.6±88.7	361.7±167.6	0.001
Total cholesterol (mg/dl)	112.1±25.37	124±36.11	0.113
Na^+ (mmol/L)	135 ±4.74	134.7 ±5.81	0.80
K^+ (mmol/L)	3.59 ±0.55	3.68±0.62	0.50

Out of 100 patients, 2 patients expired. Both of them were having thrombocytopenia, low hematocrit, deranged renal and hepatic parameters, hypoalbuminemia, raised LDH and hypertriglyceridemia. Both of them developed multi organ dysfunction syndrome and shock requiring oxygen therapy and vasopressor support.

Fig 3: Eschar on anterior abdominal wall

Discussion

The present study was conducted on 100 patients admitted in medicine wards of Government Medical College and hospital, Kota with acute febrile illness and diagnosed to have Scrub typhus by IgM ELISA method.

Most of the patients (41%) belong to the age group 41-60 years. Females are more affected than males (female: male =1.5:1). This goes in line with the results of other studies. In a study by *Inamdar et al* [4]. 37.5% belonged to 41-60 years age group. Female to male ratio was 1.06:1 and 1.05:1 in studies conducted by *James Philomen et al* [5]. and *Sharma et al* [6]. respectively. Middle aged females are key workers in both household and agricultural fields in typical Indian families especially from rural areas. Grass cutting, crop sowing and harvesting, type of work in farms with bare hands and sometimes barefoot also with typical squatting posture in the field areas predisposes them to bite exposure of infected mite from soil and scrub vegetation. Work related to animal husbandry such as cattle bathing and milking also exposes them to mite inhabiting the animal skin. Traditional dressing pattern of females also may be a contributing factor for more exposure to mite bite due to open and loose type of clothing.

In our study, 85% patients belonged to rural areas whereas 15% patients belonged to urban area. *Saha et al* [7]. also found that 78.6 % patients were from rural area and 21.4% were from urban area. Scrub typhus more commonly affects rural population as they are more engaged in occupational or recreational activities that brings them into contact with mite-infested habitats such as bushes and grass. The habit of sitting and sleeping directly on soil ground or *kachcha* houses in the field areas also makes them more prone to be bitten by mites. Prevalence is more in farmers and agriculture workers (65%). *Saha et al* [7]. also observed that majority of patients were agricultural workers (35.7%) followed by housewives (28.6%), businessmen (21.4%) and students (14.3%). *Inamdar et al* [4]. also found that maximum patients (35.5%) were farmers/agricultural labourers.

The most common manifestation is fever seen in 100% patients, followed by body ache (68%), headache (56%), breathlessness (48%), abdominal pain (48%), cough (46%), nausea/vomiting (41%), jaundice (34%), decrease urine output (26%), diarrhea (9%), altered sensorium (9%) and convulsions (2%). *Philonema et al* [5], *Peesapati et al* [8]. and *Narlawar et al* [9]. also reported fever as the most common symptom. *Das et al* [10]. observed cough and shortness of breath in 47.54% cases, abdominal pain and vomiting in 40.59% cases and altered sensorium in 9.9% cases similar to our study, whereas *Sharma et al* [6]. observed, breathlessness in 42% cases, abdominal pain in 28%, altered sensorium in 24%, vomiting in 23%, cough in 15% and convulsions in 7% cases. In our study, maculopapular rashes on the trunk were seen in 5% cases. Rash usually becomes apparent after 3-5 days of onset of symptoms and blanches within a few days. *Dodake N et al* [11]. also observed maculapapular rashes in 4% cases.

Physical examination revealed hepatomegaly in 64% patients followed by splenomegaly (36%), pleural effusion (13%), ascites (13%) inguinal lymphadenopathy (3%) and generalized lymphadenopathy (5%). O. tsutsugamushi primarily infects endothelial cells and macrophages, disseminates into multiple organs via hematogenous and lymphatic routes, and predominantly localizes in the macrophages of liver and spleen, which explains organomegaly and lymphadenopathy [12]. The possible reason for serositis is vascular leakage and hypoalbuminemia [13]. *Das et al* [10]. observed hepatomegaly in 55.45% patients followed by splenomegaly in 55.45% and lymphadenopathy in 3% patients. *Sharma et al* [6]. observed hepatomegaly in 61% patients, splenomegaly in 45% and lymphadenopathy in 11% patients.

An eschar at the bite site of the mite is pathognomic of scrub typhus which is usually painless and non-pruritic[1]. Eschar was found in only 12% cases in our study, though its frequency varies from 7 to 80% (Figure 3). The usual sites of eschar were anterior abdominal wall (6%), medial aspect of thigh (4%) and axilla or groin (2%). *Sharma et al* [6]. and *Jamil et al* [14]. found eschar in 14% and 27.8% cases respectively. Detection of eschar in less number of cases in present study might be due to dark complexion leading to poor visibility or small eschar overlooked by the examiner. Patients themselves also may ignore this small bite as general

insect bite of mosquito or injury mark. Moreover, this bite mark may not be associated with any noticing symptom mainly fever which usually appears around 1 week later, hence may not seek attention of the patient or some may not disclose even. Also, extensive thorough search for eschar was not possible in majority of females considering their privacy and legal issues.

Laboratory profile revealed hypertriglyceridemia (92%), increased LDH (89%), low hematocrit (80%), thrombocytopenia (77%), hypoalbuminemia (61%), anemia (Hb<11gm%) in 60%, leukocytosis (31%) and neutrophilia (29%). *Philonema et al* [5]. found thrombocytopenia in 56%, anemia in 44%, leukocytosis in 23%, deranged KFT in 22% and hyperbilirubinemia in 18%. *Jamil et al* [14]. found hyperbilirubinemia (62.7%), anemia (35.59%), raised ALP (33.5%), thrombocytopenia (33.33%), leukocytosis (27.12%) and deranged KFT (27.12%). *Das et al* [10]. observed elevated SGOT in 95.3%, raised SGPT in 73.4%, hypoalbuminemia in 85.4% and leukocytosis in 47.87%. *Saluja M et al* [15]. described elevated serum LDH in 43.75% and hypertriglyceridemia in 50% cases.

We observed acute hepatic dysfunction as the most common complication, seen in 52% cases. The mean total bilirubin was 3.415±4.46 mg/dl. The mean SGOT and SGPT were 185±187.4 and 114.6±126.8 mg/dl respectively. *Sharma et al* [6] and *Sinha et al* [16]. also described acute hepatic dysfunction as the most common complication in scrub typhus, present in 61% and 94.65 cases respectively.

Acute kidney injury (AKI) was seen in 36% patients in our study. The mean urea and creatinine levels were 78.76±78 mg/dl and 2.02±2.11mg/dl respectively. *Sharma et al* [6]. and *Sinha et al* [16]. described AKI in 32% and 26.1% patients respectively. AKI can occur in scrub typhus because of renal hypoperfusion due to shock and volume depletion, disseminated vasculitis and acute tubular necrosis due to direct invasion by O. tsutsugamushi.

We found multi organ dysfunction syndrome (MODS) in 35% cases which was nearly similar to studies by *Varghese et al* [3]. (34%) and *Sharma et al* [6]. (25%). As *O. tsutsugamushi* infects vascular endothelium leading to disseminated vasculitis and perivascular inflammatory lesions, resulting in significant vascular leakage and multi organ dysfunction.

Acute respiratory distress syndrome (ARDS) occurred in 32 patients (32%) in our study. *Narlawar et al* [9]. and *Varghese et al* [3]. also found ARDS in 34.5% and 33.7% respectively.

In our study, encephalitis was seen in 7% cases which is similar to studies conducted by *Jamil et al* [14]. (8.47%), *Inamdar et a* [4]. (8.5%) and *Narlawar et al* [9] (10.4%). Shock (systolic BP<90mmHg) was found in 7% cases in our study. *Sinha et al* [16] observed shock in 14% cases. Myocarditis was seen in 4% cases who developed chest discomfort and breathlessness associated with ST-T changes on ECG, later comfirmed by 2-D echocardiography. Different studies have reported variable prevalence of myocarditis. *Narvencar et al* [17] and *Kim et al* [18] observed myocarditis in 6.7% and 2.4% patients respectively.

Out of 100 patients, 2 patients expired giving a mortality rate of 2%. Mortality rate in scrub typhus varies from less than 1% to up to 30% if left untreated. *Saluja et al* [15], *Philonema et al* [5] and *Sinha et al* [16] described mortality rates of 3.75%, 6% and 16.6% respectively in their studies. Less mortality rate in our study might be due to early suspicion of diagnosis and rapid confirmation by ELISA test leading to early initiation of treatment. Early initiation of type B treatment protocol containing chloramphenicol in non responders in our study group, can also explain the lesser mortality in comparison to above studies. A study by Balasubramanian P *et al* [19]. found resistance to doxycycline in 11.4% cases and showed response to chloramphenicol.

Both the patients who expired were having thrombocytopenia, low hematocrit, deranged renal and hepatic parameters, hypoalbuminemia, raised LDH and hypertriglyceridemia. They were having multi organ-system dysfunction namely, ARDS, hepatic dysfunction, AKI and shock requiring oxygen therapy and vasopressor support. Both of them expired within 24 hours of hospitalization. *Varghese et al* [3]. described these complications to be significantly associated with mortality.

There is no association of severity with age, gender, region and presence of eschar. Severity of disease is significantly associated with thrombocytopenia (p=0.040), anemia (p=0.008), lower hematocrit (p=0.00), leucocytosis (p=0.008), hypoalbuminemia (p=0.03), hypertriglyceridemia (p=0.000) and raised serum LDH (p=0.03). *Kim et al.*[18] in his study described leucocytosis (p=0.001) and low albumin level (p=0.004) to be significantly associated with severity of disease. Sivaprakasam E *et al* [20]. found anemia, thrombocytopenia, elevated transaminases, and hypoalbuminemia to be predictors of severity of disease.

Conclusion

Scrub typhus should be considered in patients presenting with acute febrile illness associated with hepatosplenomegaly, thrombocytopenia, hypertriglyceridemia, elevated liver enzymes, renal dysfunction or ARDS, with or without the presence of eschar. Due to the varied presentation and high mortality owing to its complications, a high index of suspicion is required for early diagnosis and treatment to prevent morbidity and mortality.

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