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Original Research Article

Clinical and biochemical profile of scrub typhus patients with emphasis on liver dysfunction in a tertiary care centre in South Rajasthan

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ABSTRACT

Background: Scrub typhus is a zoonotic infectious disease presenting commonly with acute febrile illness of variable severity and symptoms. It mimics other more prevalent tropical febrile illnesses such as dengue, malaria, and leptospirosis. Prevalence is high in and around Udaipur due to hilly terrains and agricultural farmlands. Multisystem involvement is common but liver dysfunction is a fatal comorbidity.
Methods: In a retrospective observational study, we analyzed the clinical, biochemical, and demographic parameters of 85 patients of scrub typhus. The study population was distributed into four groups for abnormal liver chemistries based on American College of Gastroenterology (ACG) clinical guidelines: normal, borderline high, mild elevation, and moderate elevation.
Results: Almost 80% of patients had abnormal liver chemistries including either serum bilirubin or transaminases. More than 30% of patients were categorized in group 2 and group 3 of the abnormal liver chemistries. Group 4 with moderate to severe liver dysfunction had 15.3% (n=13) patients. Thrombocytopenia and elevated blood urea and Creatinine were significantly seen in patients with both scrub typhus and liver dysfunction.
Conclusions: Thus, in our study prevalence of hepatitis and jaundice with multiorgan failure in scrub typhus patients was significantly high. Timely identification of systemic complications and screening of liver chemistries on presentation is of utmost importance for better outcomes, among seriously ill patients.

Keywords: Scrub typhus, Hepatic dysfunction, Eschar, Hepatorenal syndrome, Liver chemistries

INTRODUCTION

Scrub typhus is a zoonotic infectious disease presenting most commonly with acute febrile illness of variable severity and symptoms. It is now one of the most prevalent tropical illnesses in some parts of India. Famously known as Tsutsugamushi disease, its prevalence and distribution has been rapidly changing in the past two decades. Scrub typhus disease is caused by gram negative obligate intracellular organism *Orientia tsutsugamushi*. It is transmitted by the bite of larva of trombiculid mites or chiggers. Rodents are definitive host from where it can be transmitted to man as accidental host.[1]

Originally described to be prevalent in Tsutsugamushi triangle spanning the Indian subcontinent, Eastern Asia and the West Pacific (Japan, India, Pakistan, Taiwan, Southeast Asia and Australia.[2] It spreads mainly during autumn and monsoon seasons from July to October. India has recently seen a drastic shift in prevalence in many parts

of North India including Rajasthan.[3,4] South Rajasthan districts are having maximum number of cases including Udaipur.

Scrub typhus is an acute febrile illness with varying severity. Initial symptoms can mimic any other febrile illness with overlapping symptoms like fever, headache, myalgia, respiratory and gastrointestinal symptoms. In areas with high prevalence of dengue, malaria and typhoid, it is difficult to detect scrub typhus on the basis of history and initial clinical examination.[5] A typical eschar can be seen in up to 7 to 80% of cases depending on the local epidemiology and skin complexion.[6] Severity of illness ranges from mild febrile illness to severe systemic involvement from fulminant hepatitis, encephalitis and acute respiratory distress syndrome.[7] Complicated scrub typhus includes clinical features like thrombocytopenia, renal dysfunction, altered sensorium, jaundice, septic shock and myocarditis. Multi organ involvement is quite frequent in scrub typhus infection, thus is the incidence of thrombocytopenia.[8,9] However severity of infection cannot be easily judged by degree of thrombocytopenia. Liver dysfunction is classified into following categories, as recommended by the American College of Gastroenterology (ACG) clinical guidelines- evaluation of abnormal liver chemistries: borderline AST and/or ALT <2X upper limit of normal range (ULN), mild AST and/or ALT elevation 2 to 5 X ULN, moderate AST and/or ALT elevation 5 to 15 X ULN, severe AST and/or ALT elevation more than 15 X ULN, and massive AST and/or ALT >10,000 IU/l.[10] Prerenal azotaemia and Acute kidney injury (AKI) is a known complication with unknown links to severity of liver disease.

We thus intend to evaluate the same through this project in all serological positive cases of scrub typhus patients admitted to Pacific Medical College and Hospital, Udaipur, Rajasthan with especial focus on hepatic dysfunction and its correlation with other factors of morbidity like haematological and renal dysfunction.

METHODS

Study population

Patients admitted with confirmed diagnosis of Scrub typhus using clinical and serological methods at Pacific Medical College and Hospital (PMCH), Udaipur, Rajasthan from July 2023 to November 2023.

Study design

It was a retrospective observational study.

Inclusion and exclusion criteria

All clinically suspected patients with an acute febrile illness and confirmed with scrub typhus infection as final diagnosis were included in this study. All demographic data, detailed history, past treatment history/any comorbid illnesses were recorded in a study proforma. Relevant physical examination, vital signs and relevant investigations were also noted from medical records. Scrub typhus serology was tested for IgM antibodies to *Orientia tsutsugamushi* using solid phase immunochromatographic based rapid test kits standard Q card method-SD biosensor). Other haematological and biochemical parameters including complete blood count, fasting blood sugar, renal function and liver function tests were also recorded. Patients with malaria, dengue fever, viral pharyngitis, enteric fever and urinary tract infection were excluded through history, clinical examination and appropriate laboratory investigations. Acute viral hepatitis A, B and C were also be ruled out by specific investigations.

In present study population with scrub typhus disease or infection according to lab investigations (liver enzymes ALT and AST) data was distributed in following four groups for abnormal liver chemistries based on ACG guidelines (Table 1).[10]

Table 1: Predefined groups for abnormal liver chemistries based on ACG guideline.

Groups	Range according to group
Group I (normal)	ALT/AST less than upper limit of normal reference range (<49 IU/l)
Group II (borderline high)	ALT/AST elevation less than 2 X ULN (more than >49 to ≤98 IU/l)
Group III (mild elevation)	AST/ ALT elevation 2 to 5 X ULN (>98 and <245 IU/l)
Group IV (moderate elevation)	AST/ ALT elevation 5 to 15 X ULN (≥245 and <735 IU/l)

Data collection and statistical analysis

Data of all study population was collected from hospital records and lab records by the primary investigators. In statistical analysis, normality of the data was checked using the Kolmogorov–Simonov test. Computer-based statistical software, statistical package for social sciences (SPSS) version 23, was used for Kruskal–Walli's test for multiple comparisons of Hb, total leucocyte count, platelet count, total bilirubin, serum urea and creatinine respectively, for predefined groups. For all statistical analyses, the p value <0.05 was considered the lowest level of significance.

The study protocol was approved by the institutional ethics committee on 01.12.2023 (IEC/255/2023) and informed consent was obtained from the patients.

RESULTS

Based on the above-mentioned inclusion and exclusion criteria a total of 85 patients were enrolled in the study. Mean age of the subjects was 49 years with 51.7% males

and 48.3% females. The cases from rural households were 87% in comparison to city dwellings were only 13%, indicative of less incidence in populated urban areas with better hygiene and sanitation. The demographic parameters of the study subjects are shown in Table 2 respectively.

Table 2: Distribution of demographic data and clinical profile of 85 patients with scrub typhus included in the study.

Variables	Number of patients	Percentage
Age (in years)		
<30	15	17.6
30-60	48	56.5
>60	22	25.9
Gender		
Male	44	51.7
Female	41	48.3
Residence		
Rural	74	87
Urban	11	13

When comparing the clinical characteristics amongst all 85 cases it was evident that 93% (n=79) patients had fever at presentation in present study (Figure 1). The remaining 6 patients did not develop fever during period of hospitalisation. Most of the patients were already on antipyretics or were in the convalescent phase of infection. Although fever is an essential diagnostic and clinical sign of scrub typhus but some diabetic, elderly or immunosuppressed patients may not present with obvious fever. Other constitutional symptoms including cough and myalgia were present in more than 50 patients. Gastrointestinal symptoms like abdominal pain and nausea were seen in 57.6% (n=49) and 40% (n=34) patients.

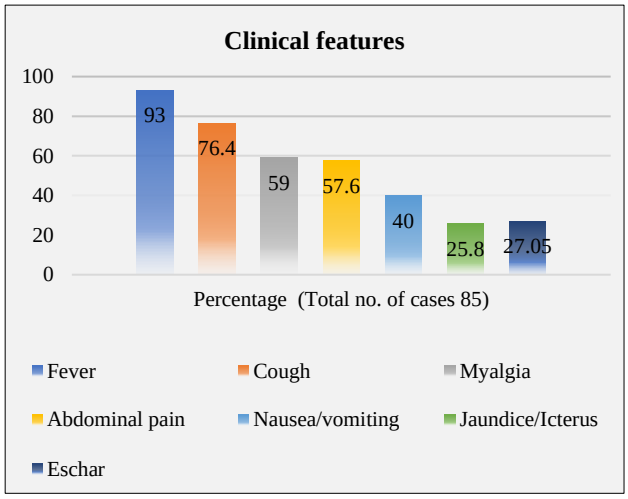

Figure 1: The distributions of clinical features.

Clinical jaundice or icterus was visible in 25.88% (n=22) patients which was later confirmed by serum bilirubin estimation. Eschar mark was only seen in 27% of patients. Thus, it is a pathognomonic but uncommon finding in scrub typhus only seen in less than two third of patients. Severe systemic manifestation including altered sensorium was seen in 5.8% (n=5) of patient population which indicated neurological involvement in scrub typhus disease. CSF studies were warranted to rule out active meningoencephalitis in these cases but was not performed as rapid improvement was seen with ongoing treatment. Graphical illustration of the clinical feature in scrub typhus patients was shown in Figure 1.

Haematological and biochemical profile of patients is shown in Table 3 with respective mean values. Mean haemoglobin levels and platelet count were recorded also on the lower side with mean values of 11.53±1.84 g/dl and 139476.2±88805.63 cells/cumm respectively. More than 50% of patients had normal Total leucocyte counts (Table 4). Serum bilirubin levels was raised in 25.88% (n=22) patients with mean values of 1.64±1.57 mg/dl for total and 1.27±1.23 mg/dl for direct bilirubin respectively. Mean values of AST and ALT were 128.61±123.92 IU/l and 91.34±67.96 IU/l respectively indicating liver injury in almost majority of patients of scrub typhus. Hence, deranged kidney function tests were also observed with high mean blood urea levels (60.4±55.8 mg/dl) and serum creatinine (1.37±1.30 mg/dl) in this study besides abnormal liver chemistries (Table 4).

Table 3: Hematological and biochemical profiles of patients.

Parameters	Normal reference range	Mean±SD
Hematological parameters		
Hemoglobin	g/dl	11.53±1.84
WBC count	4000-11000 (cells/cumm)	9463.88±4153.88
Platelet count	150000-400000 (cells/cumm)	139476.2± 88805.63
Biochemical parameters		
Total bilirubin	0.2-1 (mg/dl)	1.64±1.57
Direct bilirubin (mg/dl)	0.1-0.3 (mg/dl)	1.27±1.23
AST/SGOT	9-49 (IU/l)	128.61±123.92
ALT/SGPT	9-49 (IU/l)	91.34±67.96
ALP	38-126 (U/l)	240.98±201.3
Urea	10-49 (mg/dl)	60.4±55.8
Creatinine	0.5-1.1 (mg/dl)	1.37±1.30

In this study we did not find any patient in the categories of severe and massive AST/ALT elevation according to the American College of Gastroenterology (ACG) clinical guidelines- evaluation of abnormal liver chemistries (Table 1). Therefore, patient population distribution was planned in four groups including normal to moderate elevation of AST/ ALT concurring to result. The study population was distributed in four groups as per abnormal liver chemistries as per the standard ACG criteria mentioned above. Similar is illustrated in Table 5.

Table 4: Distribution of patients with deranged hematological and biochemical parameters.

Parameters	No. of cases	Percentage (n=85)
Hemoglobin <11 g/dl	30	35.29
Total leucocyte count (thousands/cumm)		
<4000	5	5.88
4000 -11000	53	62.35
>11000	27	31.76
Platelet count <150000/cumm	48	56.47
Elevated total bilirubin level (>2 mg/dl)	22	25.88
Increased serum urea (>45 mg/dl)	35	41.17
Increased serum creatinine (>1.5 mg/dl)	17	20

Table 5: Distribution of abnormal liver chemistries for predefined groups.

Groups	Range according to group	Number of patients (n=85) (%)
Group I (normal)	ALT/AST less than upper limit of normal reference range (<49 IU/l)	18 (21.17)
Group II (borderline high)	ALT/AST elevation less than 2 X ULN (more than > 49 to ≤98 IU/l)	28 (32.94)
Group III (mild elevation)	AST/ ALT elevation 2 to 5 X ULN (>98 and <245 IU/l)	26 (30.58)
Group IV (moderate elevation)	AST/ ALT elevation 5 to 15 X ULN (≥245 and <735 IU/l)	13 (15.29)

The normality of the data was checked using the Kolmogorov–Simonov test for various lab parameters. The data for haemoglobin (Hb), total leucocyte count (TLC) and platelet count (P/C) of the study population was normally distributed (K–S test statistic D value=0.08757, 0.11275, 0.08065 and p value=0.50445, 0.2134, 0.60908 respectively), and data for Total bilirubin (T. Bil), ALT, AST, urea and creatinine was not normally distributed (D value=0.18371, 0.15491, 0.22422, 0.23124, 0.27469 and p value=0.00553, 0.03014, 0.00031, 0.00017, <0.00001 respectively).

The haematological lab parameters including Hb, TLC and platelet count data of present study population were normally distributed; however, number of patients was found less than 30 in each predefined group for abnormal liver chemistries. Therefore, the Kruskal–Walli's test was conducted for predefined four groups of present study (Table 6). The result of the Kruskal–Walli's test was statistically significant (p value=0.002) only for platelet count in haematological parameters (Figure 2). However, multiple comparisons of Hb and TLC for predefined four groups were performed by the Kruskal–Walli's test, which was not significant (p value=0.228 and 0.504 respectively).

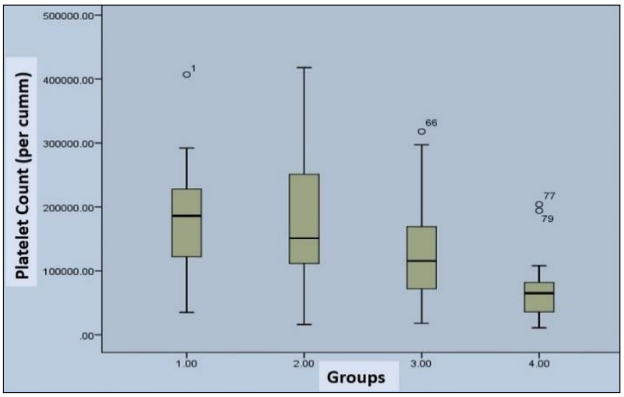

Figure 2: Multiple comparison of platelet count (per cumm) in predefined four groups for abnormal liver chemistries: normal, borderline high, mild elevation, and moderate elevation.

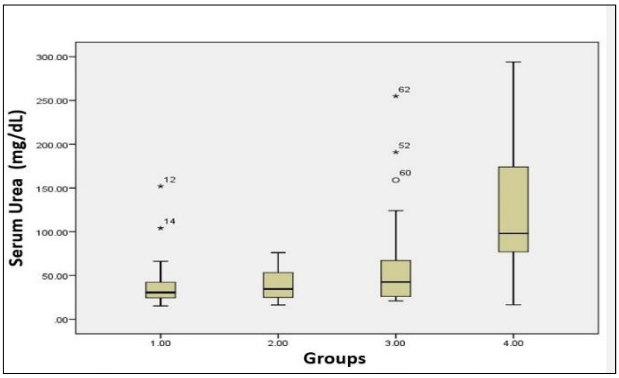

Figure 3: Comparison of serum urea (mg/dl) in predefined four groups for abnormal liver chemistries: normal, borderline high, mild elevation, and moderate elevation.

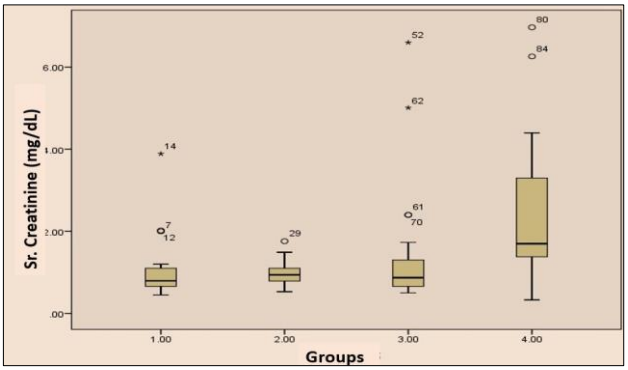

Figure 4: Comparison of serum creatinine (mg/dl) in predefined four groups for abnormal liver chemistries: normal, borderline high, mild elevation, and moderate elevation.

The biochemical parameters including serum urea and creatinine were not normally distributed; hence, the Kruskal–Walli's test was conducted for predefined four groups (abnormal liver chemistries) in study subjects (Table 6). The results of the Kruskal–Walli's test was statistically significant for serum urea and serum creatinine (p value=0.001 and 0.004 respectively) as illustrated in Figures 3 and 4.

Table 6: Comparison of hematological parameters (hemoglobin, TLC and platelet count) and biochemical parameters (serum urea and creatinine) between the predefined groups for abnormal liver chemistries (all variables are presented as mean±SD).

Parameters	Group I: normal	Group II: (borderline high)	Group III: (mild elevation)	Group IV: (moderate elevation)	P (significant <0.05)
Hemoglobin (g/dl)	12.14±1.60	11.84±1.97	11±1.75	11.23±1.40	Kruskal–Walli's test (p=0.228)
TLC (thousands/mm^3)	10428±5919	9594.6± 3474.4	8586±3843	9791±3799	Kruskal–Walli's test (p=0.504)
Platelet count (per mm^3)	173444±96323	171357±90143	126077±79148	77384.6±60603	Kruskal–Walli's test (p=0.002)
Serum urea (mg/dl)	42.7±34.0	39.13± 18.15	63.15±58.5	125.67±78.3	Kruskal–Walli's test (p=0.001)
Serum creatinine (mg/dl)	1.08±0.83	0.96±0.27	1.37±1.41	2.65±2.06	Kruskal–Walli's test (p=0.004)

DISCUSSION

Scrub typhus is a tropical infection caused by the rickettsial gram negative bacterium *Orientia tsutsugamushi*. The vector is the chigger larva of Leptotrombidium mite that inhabits low lying shrub vegetation.[16] Natural life cycle involves transmission between vector and some mammals or birds. Disease in humans is a result of accidental transmission. The prevalence was previously confined to the 'Tsutsugamushi triangle' (North Japan to far east Russia, North Australia and Afghanistan in west) and it has traditionally been considered to be a disease of rural and agricultural households.[17]

It is often acquired during recreational, occupational or agricultural exposure because crop fields are an important reservoir for transmission. After an incubation period of 1–2 weeks, it usually presents with symptoms like high-grade fever with chills, myalgia, headache, cough, generalized lymphadenopathy, jaundice, and gastrointestinal symptoms, following a typical black eschar at the bite site.[18] The disease process is thought to involve disseminated vasculitis and peri-vascular inflammation, leading to significant plasma leakage and end-organ dysfunction and ultimately multiple organ dysfunction syndrome.[19] Hepatic injury is frequently with mild hepatitis, hyperbilirubinemia, coagulopathy, and rarely fulminant hepatic failure.[20] Histopathological findings at autopsy revealed submassive hepatocellular necrosis, inflammatory cell infiltration in Glisson's capsules, and sporadic fibrin thrombi in the hepatic sinusoidal cells indicating disseminated intravascular coagulation.[21] Regarding liver involvement, it is uncommonly mentioned in the Western literature. "No consistent liver enzyme abnormality" is even shown in Western medical textbooks. In the Asian studies also, it is uncommon to focus on a relationship between scrub typhus, abnormal liver functions and multiorgan failure.

Lately, there have been many outbreaks in India reported from the states of Himachal Pradesh, Uttarakhand, Rajasthan, New Delhi, Chandigarh, Goa, Andhra Pradesh and Meghalaya.[12,22,23] South Rajasthan is now an endemic hotspot for Scrub typhus due to increased colonisation and merging of urban and hilly/rural terrains in the foothills of Aravalli ranges. There have been numerous reports of increased prevalence of Scrub Typhus in South Rajasthan districts like Kota, Udaipur, Chittorgarh and Rajsamand lately.[13,24]

Various clinical aspects and demographic characteristics have been studied in the existing literature. Special focus of liver dysfunction has also been mentioned in some studies conducted in India and abroad.[25-28]

None of the researchers have studied the detailed relationship of severity of liver dysfunction with renal and haematological parameters. It is important to link all these biochemical and clinical manifestations in term of predicting output and prognosis in this fatal illness. We have tried the same with data analysis in 85 patients who were divided in various predefined subgroups as per the ACG criteria of abnormal liver chemistries.

This study was retrospectively conducted on a group of 85 patients admitted in PMCH institute during the period of July to November 2023 which is the peak transmission phase of scrub typhus in Udaipur. Subgroup analysis was made according to the ACG classification of liver dysfunction as mentioned prior. Majority of patients were in the middle age group between 30 to 60 (51.8%) which

correlates well with the working population exposed to outdoor activities. Female to male ratio was almost similar as both genders are equally involved in agricultural and livestock activities in this region. 87% of patients were from rural background which was similar to results of previous study conducted in Hadoti region by Jain et al.[13]

Fever (93%), myalgia (59%) and cough (76.4%) were the predominant symptoms followed by gastrointestinal symptoms in the form of pain (57.6%) and vomiting (40%). These results were concordant with previous studies such as Jain et al and Verma et al.[13,14] Clinical signs like Icterus and Eschar were seen in less than one-third of patients which is in concordance with some studies as it might be less evident due to the dark complexion in south Asian patients.[8,29] The clinical characteristics were more or less similar across different regions of the country with little variations in severity as described by previous studies by Takhar et al, and Dodake al.[11,30]

Results after final analysis of clinical and biochemical characteristics of 85 patients and their records revealed that liver dysfunction was present in almost 89% (n=75) patients in the form of either elevated total bilirubin or liver enzymes. This finding is consistent with the results of Yang et al, Hu et al and Shrestha et al.[28,31,32] Hyperbilirubinemia (total serum bilirubin >2 mg/dl) was found in more than 25% of patients. More than 30% patients were categorised in group 2 and group 3 of the abnormal liver chemistries. Group 4 with moderate to severe liver dysfunction had 15.3% (n=13) patients (Table 5).

Majority of patients with mild (grade3) or moderate (grade 4) grade of liver dysfunction had significant reduction in the platelet counts ($p<0.05$) (Table 6). Thrombocytopenia, thus can be a useful marker of prognosis along with hepatic impairment. APRI (AST to platelet ratio index) is a similar parameter used in in liver fibrosis patients.[33] Similar index can be studied in hepatitis due to infective tropical illnesses. Similarly, there was significant elevation of blood urea and serum creatinine in similar subgroups. Thus, patients with liver dysfunction and severe scrub typhus were also prone to renal impairment and vice-versa. Pathophysiology might be associated with prerenal azotaemia due to renal hypoperfusion and volume depletion.[34] Severity of liver dysfunction directly correlated with the impaired platelet count, creatinine and urea values as shown in results.

Thus, scrub typhus should be viewed as a constellation of multisystemic disorder with aggressive approach targeting individual organ dysfunction rather than a general supportive care. A scoring system for severity should be developed using the above mentioned biochemical and haematological parameters. It will be very helpful for clinicians in triage of patients for immediate, timely and aggressive management during admission. Patients with more than a week of illness and predisposing immunosuppressive condition or liver disease can rapidly land into fulminant hepatic failure which has very high mortality. Thus, history taking and ruling out any hepatotoxic factor is of utmost important. The primary treatment is in the form of doxycycline which is a hepatotoxic drug itself. Careful selection of hepatoprotective drugs and safer antibiotics is required. The limitations of the study were due to its cross- sectional nature and non-availability of outcomes with treatments. However, a lot of valuable information could be derived retrospectively to further strengthen the results and plan an outcome centred study in future.

CONCLUSION

Scrub typhus is one of the most prevalent zoonotic diseases in South Rajasthan including Udaipur district. Prevalence of hepatitis and jaundice with multiorgan failure in scrub typhus patients was significantly high. Timely identification of systemic complications and screening of liver chemistries on presentation is of utmost important for better outcomes, among seriously ill patients. Careful selection of the hepatoprotective drugs and safer antibiotics is required to avoid further liver injury. Kidney dysfunction goes parallel to liver dysfunction as seen in enrolled patients ultimately increasing risk of hepatorenal syndrome. Grading system for severity of scrub typhus patients on the basis of clinical and biochemical parameters is the need of the hour.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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