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Predictors of scrub typhus: a study from a tertiary care center

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ABSTRACT

Objective: To document the clinical and laboratory findings of scrub typhus infection and to determine the prognostic factors of the disease.**Methods:** Retrospective data were collected from 96 patients with scrub typhus infection, from January 2012 to December 2013, at Yashoda hospital, Hyderabad. Prognostic factors for severe scrub typhus were analyzed by a multivariate analysis.**Results:** Out of 96 patients, men were 47 (48.9%) and median age was 39 years. Patients with low socioeconomic status were 53 (55.3%). Among the 96 patients 46 (47.9%) had severe scrub typhus, 50 (52.1%) had mild severe scrub typhus. Two patients (2%) died. Symptoms of cough ($P=0.001$), presence of eschar ($P<0.001$), Glasgow coma scale (GCS) below 12 (0.04), hepatomegaly ($P=0.0001$), splenomegaly ($P=0.0001$), and meningoencephalitis ($P=0.01$), were significantly associated with severe scrub typhus. Multivariate analysis showed presence of eschar (odds 2.5; 95% confidence interval (CI) 1.1–8.5), hepatomegaly (odds 1.9; 95% CI 1.1–3.8), meningoencephalitis (odds 4.8; 95% CI 1.1–21.8), GCS<12 (odds 1.8; 95% CI 0.5–2.4) and cough (odds 1.5; 95% CI 0.7–3.5) to be significantly associated with severe scrub typhus.**Conclusions:** In our study, eschar, hepatomegaly, meningoencephalitis, poor GCS and cough were significantly associated with severe scrub typhus.

1. Introduction

Scrub typhus is a rickettsial disease caused by *Orientia tsutsugamushi* (formerly called *Rickettsia tsutsugamushi*), an obligatory intra-cellular Gram-negative bacterium[1]. It can be transmitted to human and other vertebrates by the bite of an infected larval trombiculid mite (chigger)[2]. It is widespread, especially seen in the so called “tsutsugamushi triangle,” which includes Australia, Japan, Taiwan, China, South Korea, the islands of the Western Pacific region, Indonesia and Indian subcontinent[3]. Scrub typhus is endemic in India and has been reported from all parts of

north, east and south India[4–6]. Recent reports from several parts of India have noted an increase in the incidence of scrub typhus[7]. Majority of people affected with scrub typhus, are those working in agriculture fields works, oil palm and rubber plantations workers, and belong to low-socioeconomic population[8,9].

Scrub typhus presents as an acute febrile illness with constitutional symptoms, rashes, myalgias, and headache. It may involve the tissues of any organ system and can lead to organ dysfunction and these include kidney (acute renal failure), liver (hepatitis), lungs (acute respiratory distress syndrome), central nervous system (meningitis), or may cause circulatory collapse with haemorrhagic features[10]. Scrub typhus is under-diagnosed, as its clinical features are non-specific, diagnostic facilities are not easily accessible, and most clinicians have a low index of suspicion for this disease[11]. The aim of the study was to retrospectively analyze clinical features, risk factors, disease severity and

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mortality in patients with scrub typhus from the medical records of patients admitted to this tertiary educational hospital for the last two years.

2. Materials and methods

Patients diagnosed with scrub typhus and admitted in Department of Medicine, Yashoda Hospital Malakpet, Hyderabad, were included in this study. Yashoda Hospital is a referral center in South India, the states of Andhra Pradesh and Telangana. Scrub typhus was diagnosed based on the modified definition given by the World Health Organization^[11]. We collected the data retrospectively, of all scrub typhus cases in the study period from January 2012 to December 2013. During the two years, 130 patients diagnosed to have scrub typhus were initially selected. Out of the 130 patients, 15 patients had incomplete laboratory tests data and 19 patients did not have clear diagnosis. Remaining 96 patients' were included in the study and their data were collected. This study was approved by the Institutional Scientific Committee.

Patient's medical history (clinical and physical examination), reports of laboratory investigations, including complete blood count, serum creatinine, blood urea, serum albumin, serum glucose, liver function tests, urine analysis (including urine albumin), abdominal ultrasound, cerebrospinal fluid (CSF) analysis and chest X-rays were collected from medical records for all patients. Twenty (20.8%) patients had CT scan brain, 15 (15.6%) patients underwent magnetic resonance imaging of brain and these were performed as per the clinician's discretion. Electroencephalogram was done in 25 (26%) patients. Out of 96 scrub typhus patients, 2 patients succumbed to the disease. Two groups were divided in this study— mild disease and severe disease of scrub typhus^[12–15].

2.1. Serological examination

In the present study, Weil–Felix test was performed in all patients (100%) as it is economical yields rapid results (low sensitivity and specificity) and immuno–chromatographic test (ICT) was performed in 85 (88.5%) patients. This is a rapid diagnostic test with sensitivity of 97.6% and specificity of 72% for scrub typhus.

2.2. Statistical analysis

Statistical analysis was performed using SPSS 13.0 software (statistical package for the Social sciences, SPSS Inc). Mean \pm SD were calculated. The paired *t* test was applied to test the differences in continuous variables. Univariate and multivariate analysis was performed for potential confounders age, gender, cough, chest X–ray abnormal, blood urea, hepatomegaly, splenomegaly, Glasgow coma scale (GCS)<12,

meningoencephalitis, etc. All tests were two sided and *P* value <0.05 were considered statistically significant.

3. Results

A total of 96 patients with scrub typhus were included in the study. Men constituted 48.9% with a median age of 39 years and age range of 15–70 years. Co–morbid illness and possible risk factors hypertension, diabetic mellitus and history of smoking were seen in 25 (26%), 18 (18.7%) and 15 (15.6%) patients, respectively. Mean duration of fever before admission was (5.6 \pm 2.1) d. Most common symptoms were cough noted in 49 (51.0%) patients, abdominal pain in 42 (43.7%), nausea/vomiting in 41 (42.7%), diarrhea in 39 (40.6%), melena in 12 (12.5%), and convulsions/ seizure in 5 (5.2%) patients. On clinical examination, splenomegaly was present in 42 (42.8%), hepatomegaly in 26 (26.5%) and eschar was present in 20 (20.8%). The other demographic and features at admission are given in Table 1.

Table 1

Baseline characteristics.

Parameters	Number (n=96)
Men	47 (48.9%)
Median age years	39
Age range years	15–70
Hypertension	25 (26.0%)
Diabetic mellitus	18 (18.7%)
Smoking	15 (15.6%)
Alcoholics	10 (9.6%)
Mean duration of fever before admission (days)	5.6 \pm 2.1
Cough	49 (51.0%)
Melena	12 (12.5%)
Chest X–ray abnormal	52 (54.1%)
Eschar present	20 (20.8%)
Mean erythrocyte sedimentation rate	58.1 \pm 29.3
Platelet count <20000/mL	10 (10.2%)
GCS<12	20 (20.8%)
Increased urine serum albumin	29 (30.2%)
Creatinine>2 mg/dL	8 (8.1%)
Blood urea	40.50 \pm 4.30
Serum albumin below levels (g/dL)	30 (31.0%)
Nausea, vomiting	41 (42.7%)
Abdominal pain	42 (43.7%)
Diarrhea	39 (40.6%)
Mean alkaline phosphatase	215.22 \pm 144.80
Mean serum glutamic–oxaloacetic transaminase (SGOT)	180.3 \pm 127.2
Mean serum glutamic pyruvic transaminase (SGPT)	164.1 \pm 101.2
Convulsions/ seizure	5 (5.2%)
Headache	74 (77.0%)
Meningoencephalitis.	13 (13.5%)
CSF protein elevation	25 (26.0%)
CSF sugar elevation	30 (31.2%)
Body temperature (°C)	35.65 \pm 6.80
Systolic blood pressure (mmHg)	102.0 \pm 15.1
Diastolic blood pressure (DBP) (mmHg)	64.5 \pm 12.8
Pulse (beats/min)	106.0 \pm 29.4
Respiration (breaths/min)	27.4 \pm 9.4
Hepatomegaly	26 (26.5%)
Splenomegaly	42 (42.8%)
Low socioeconomic status	60 (62.5%)
Deaths	2 (2.0%)

We compared the clinical features between patients with severe scrub typhus and mild scrub typhus. Cough ($P=0.001$), presence of eschar ($P<0.001$), mean blood urea ($P=0.001$), hepatomegaly ($P=0.001$), splenomegaly ($P=0.001$), meningoencephalitis ($P=0.01$), CSF protein elevation ($P=0.02$), CSF sugar reduction ($P=0.021$) and lower DBP (mmHg) ($P=0.001$) were significantly associated with severe scrub typhus compared to mild scrub typhus (Table 2).

Table 2

Comparison between severe and mild disease with scrub typhus.

Parameters	Severe (n=46)	Mild (n=50)	P value
Men	20 (43.4%)	27 (54.0%)	0.4
Mean age years	40.2±12.4	38.8±13.2	0.5
Age range years	25–70	15–70	0.4
Hypertension	13 (28.2%)	12 (24%)	0.6
Diabetic mellitus	9 (19.5%)	9 (18%)	0.4
Smoking	8 (17.3%)	7 (14%)	0.8
Alcoholics	6 (13%)	4 (8%)	0.6
Cough	30 (65.2%)	19 (38%)	0.001
Melena	7 (15.2%)	5 (10%)	0.5
Chest X-ray abnormal	30 (65.8%)	24 (44%)	0.049
Eschar present	15 (32.6%)	5 (10%)	<0.001
Mean erythrocyte sedimentation rate	58.1±29.3	56.2±28.2	0.5
Convulsions/ seizure	4 (8.6%)	1 (2%)	0.7
Platelet count<20000/mL	7 (15.2%)	3 (6%)	0.5
Blood urea	42.4±13.2	38.3±11.5	0.001
Increased urine albumin	15 (32.6%)	14 (28%)	0.5
Creatinine>2 mg/dL	6 (13%)	2 (4%)	0.1
Serum albumin below levels (g/dL)	19 (43.1%)	11 (22%)	0.051
Hepatomegaly	18 (39.1%)	8 (16%)	0.001
Splenomegaly	29 (63%)	13 (26%)	0.001
Low socioeconomic status	28 (60.8%)	25 (50%)	0.2
Deaths	2 (6.5%)	0	0.9
Nausea, vomiting	20 (43.4%)	21 (42%)	0.4
Abdominal pain	19 (41.3%)	23 (46%)	0.8
Diarrhea	20 (43.4%)	19 (38%)	0.7
Mean alkaline phosphatase	215.3±154.8	214.3±134.8	0.4
Mean SGOT	186.1±124.2	174.5±128.2	0.4
Mean SGPT	170.1±99.2	158.1±101.2	0.7
Convulsions/ seizure	4 (5.2%)	1 (2%)	0.4
Headache	39 (84.7%)	35 (70%)	0.8
GCS<12	14 (30.4%)	6 (12%)	0.04
Meningoencephalitis.	11 (23.9%)	2 (4%)	0.01
CSF protein elevation	20 (43.4%)	5 (10%)	0.02
CSF sugar elevation	20 (43.4%)	10 (20%)	0.021
Body temperature (°C)	38.9±4.8	37.4±5.8	0.2
Systolic blood pressure (mmHg)	95.3±12.8	108.3±17.8	0.001
DBP (mmHg)	56.8±10.3	69.8±13.1	0.001
Pulse (beats/min)	105.0±19.4	106.0±10.4	0.6
Respiration (breaths/min)	26.7±8.8	25.6±7.2	0.5
Seasonal variation			
June–November	30 (65.2%)	28 (56%)	0.4
December–May	16 (34.7%)	22 (44%)	0.5

On multivariate analysis we noted that the major predictors of severe scrub typhus were meningoencephalitis (odds 4.8; 95% confidence interval (CI) 1.1–21.8), presence of eschar (odds 2.5; 95% CI 1.1–8.5), hepatomegaly (odds 1.9; 95% CI 0.9–3.8), GCS<12 (odds 1.8; 95% CI 0.5–2.4) and cough (odds 1.5; 95% CI 0.7–3.5) (Table 3).

Table 3

Before and after analysis of prognostic factors for scrub typhus severity.

Parameters	Before adjustment		After adjustment	
	Odds	95% CI	Odds	95% CI
Cough	3.0	1.3–7.0	1.5	0.7–3.5
Eschar present	4.3	1.4–13.2	2.5	1.1–8.5
Hepatomegaly	3.3	1.2–8.8	1.9	0.9–3.8
Splenomegaly	2.0	0.8–4.5	1.1	0.8–2.4
GCS<12	3.2	1.1–9.2	1.8	0.5–2.4
Meningoencephalitis	7.5	1.4–36.1	4.8	1.1–21.8

4. Discussion

4.1. Age

In our study we found the median age of scrub typhus patients to be 39 with an age range from 15–70 years. Similar findings were reported by Varghese *et al.* from southern part of India, in his study the mean age was 36.5 years (age range from 12–75 years)[13], while Lai *et al.* noted a mean age of 43 years in Taiwan[16]. Though there is no evidence of the disease affecting the more vulnerable age groups of children and elderly compared to middle aged people, we found that patients above 65 years of age had a higher incidence of chest X-ray abnormalities and sepsis and similar findings were noted by Wu *et al.*[1]. Older patients had several complications and high mortality compared to younger patients, this is due to the age-related changes in immune mechanisms[1].

4.2. Gender

In our study, there was no significant association with gender, women and men were equally affected. However, some Chinese studies have found significant association with men[8]. The difference in occurrence may be secondary to the fact that men are more involved in the farm work and field work than women, and thus are more at risk of chigger bite and also may depend on the traditional clothes wearing patterns in men or women.

4.3. Temperature

Although most patients had a history of fever at onset, the temperatures were normal in almost all and many had hypothermia on evaluation. The mean temperature was (35.65±6.80) °C. Several studies have noted hypothermia as a risk of severe scrub typhus[17]. However, our study found no significant association of hypothermia with severe scrub typhus (38.9±4.8) °C compared to mild scrub typhus (37.4±5.8) °C.

4.4. Eschars

Eschars have been considered to be vital diagnostic markers for scrub typhus[18]. The present study, we found a

20.8% prevalence of eschars with significant association with severe scrub typhus. Similar reports were noted from other places in India, 13.3% in Goa and 20% in Pondicherry[6,19]. Studies from the rest of the world have shown varying prevalence of eschars, 15% in northern China[20], below 10% in Thailand[21], 46% to 92% in Korea[22], 46% in South Vietnam[23], and 63% in Taiwan[1]. In China variations were noted even across different studies, 5%–34%, 84% and 100%[20,24,25]. Similarly, there is a wide variation in the presence of eschars in children with scrub typhus[26,27].

In our study eschars were present equally in both sexes (men 11 and women 9), similar distribution was noted in previous studies[20,28]. In our patients most eschars were present in skin folds on the abdomen, chest and neck. Eschars have also been reported on feet and legs in soldiers of the US army[20]. Kim *et al.* noted in his study that eschars in men were present within 30 cm below the umbilicus, while front of the chest above the umbilicus was the common site in women[22]. Some studies have noted eschars in axilla, groin, neck, waist and inguinal area[29]. Eschar is generally associated with lymphadenopathy. In our study, only two patients had lymphadenopathy and similar cases were reported by Saah *et al.*[30]. Vivekananda *et al.* noted in his study 15 patients (30%) have lymphadenopathy[5].

The varying distribution of eschars is probably due to the different dressing life styles, personal hygiene and occupational exposure, as these affect the path of the chiggers and their persistence on the body surface.

The variation in the incidence of eschars may also be due to the difference in the strains of *Orientia tsutsugamushi* causing the disease[31], underlying genetic predisposition or may be secondary to the disease load exposure since childhood, aboriginal persons of typhus–endemic areas commonly have less severe illness and eschars[21]. Lee *et al.* found the absence of eschars were risk factor for mortality[17]. Our study, on the other hand, established eschars as independent risk factors for severe scrub typhus (odds 2.5; 95% *CI* 1.1–8.5).

4.5. Serum creatinine

Serum creatinine is a marker of kidney function. In our study we found 8 (8.1%) patients with high creatinine levels (>2 mg/dL) and no significant association with severe scrub typhus. Several reports have found increased creatinine level to cause increased risk of death in scrub typhus patients[1,6,13]. Varghese *et al.* noted in his study that serum creatinine >1.4 mg% was a predictor of mortality in scrub typhus patients[13]. Our study showed 3 (3.1%) patients had acute kidney failure, but only mean blood urea was significantly associated with severe scrub typhus. Some other study was reported 36 patients (8.3%) had acute renal failure and 20% of the patients had abnormal urinalysis, and increasing proteinuria[6]. Wu *et al.* noted the acute renal failure in 6.6% was associated with septic shock[1].

4.6. Urine albumin

In the present study we noted 29 (30.2%) patients had increased urine albumin and there was no significant association with severe scrub typhus, Attur *et al.* found in study 28.6% of adults with scrub typhus had increased urine albumin[32], and 3% to 17% of children[33,34]. Some studies have found high levels of urine albumin was significantly associated with severe scrub typhus[12].

Thus, most studies have demonstrated the varying effects of scrub typhus on kidneys, the damage being primarily secondary to hypotension and septic shock, with a possible small direct impact of scrub typhus on renal physiology. A large sample size is required to address this issue.

4.7. Respiratory involvement

In our study, 52 (54.1%) patients had chest X-ray abnormalities, similar occurrence was observed in other studies[1,35,36]. Chest X-ray abnormalities included 20 (20.8%) patients with pleural effusion, 18 (18.7%) with pulmonary edema, 8(8.3%) had peribronchial infiltrate, 3 (3.1%) had reticular infiltration, one patient(1%) had cardiomegaly and 2 (2%) had air–space consolidation. Other studies have also noted cardiomegaly, pleural effusion, focal atelectasis, hilar adenopathy and pulmonary edema as manifestations of scrub typhus[35,36]. In a study of Song *et al.*, almost all patients (98.1%) had parenchymal lung lesions[35]. Wu *et al.* in his study noted that 20.6% of patients had pneumonia (air–space consolidation) or bronchitis pattern, while 27 patients (42.9%) had pleural effusion[1]. Pleural effusion is a common occurrence, with reports of incidence of 12%–55% in scrub typhus[35,36].

In our study only two patients (3.7%) had acute respiratory distress syndrome. Sinha *et al.* from Rajasthan reported 4 cases of acute respiratory distress syndrome in scrub typhus[24]. Kumar *et al.* from north India found 28 cases of acute respiratory distress syndrome in patients with scrub typhus[37]. Combination of cough and abnormal chest X-ray is a common manifestation of scrub typhus and is a poor prognostic marker[38]. In our study both presence of cough and chest X-ray abnormalities were significantly higher in the severe scrub typhus group compared to mild group. Wu *et al.* also found abnormal chest X-ray finding with cough had a significant association with severe scrub typhus[1]. On multivariate analysis, our study established cough to have an independent association with severe scrub typhus (odds 1.5; 95% *CI* 0.7–3.5), further studies are required to confirm these findings.

4.8. Central nervous system

Scrub typhus can affect both central and peripheral nervous system[39]. Central nervous system complications in scrub typhus include intra cerebral hemorrhages,

meningitis and encephalitis, causing altered sensorium, agitation, motor weakness, seizures, neck stiffness^[19], cranial nerve deficits^[40], cerebellitis^[41], infarction^[42], subdural hematoma^[43], demyelination^[44], and typhus nodules^[40]. The peripheral nervous system involvement include myelitis and Guillain–Barre syndrome^[45], brachial plexus neuropathy^[42], mononeuritis multiplex^[46], and polyneuropathy^[42]. In our study we found 74 (77%) had headache, 5 (5.2%) had seizures, 20 (20.8%) developed altered sensorium, 13 (13.5%) had clear evidence of meningitis with encephalitis. None of our patients had any peripheral nervous system manifestation. CSF analysis showed that 5 (26%) patients had CSF protein elevation and 30 (31.2%) had CSF sugar reduction and these included patients with meningitis, encephalitis, seizures and altered sensorium. Our findings were advocated by other Indian studies^[19,47,48]. Viswanathan *et al.* found in his study, 60% of scrub typhus patients had headache^[19], while in the study by Varhese *et al.*, 66 (42.8%) patients had headache, 10 (6.5%) patients had seizures and 29 (18.8%) patients meningoencephalitis^[48]. Boorugu *et al.* noted in his study that 12 (6.3%) patients had in seizures, 42 (22.2%) patients had altered sensorium with elevation of CSF protein and hypoglycorrachial^[47].

Oaks *et al.* established in study that 14% had meningeal signs^[49], and several reports have found meningoencephalitis to be a risk factor for mortality in scrub typhus^[15,50]. The present study established meningoencephalitis as an independent risk factor for severe scrub typhus (odds 4.8; 95% *CI* 1.1–21.8). Further studies are required to expand on these findings.

Drowsiness and impaired consciousness may be a manifestation of underlying central nervous system disease or may be secondary to hypotension and high systemic infection load. In our study 20 (20.8%) patients scored below 12 on GCS. Several studies have found low GCS to be significantly associated with severe scrub typhus^[51]. Our study also established GCS below 12 as an independent predictor of severe scrub typhus (odds 1.8; 95% *CI* 0.5–2.4).

4.9. Elevation of Liver enzymes

Several studies have found hepatic dysfunction in 75%–92% of scrub typhus patients^[14,15]. In our study 41 (42.7%) patients had nausea, vomiting, 42 (43.7%) had abdominal pain, 39 (40.6%) had diarrhea, 26 (26.5%) had hepatomegaly, and 42 (42.8%) patients presented with splenomegaly were presented. Viswanathan *et al.* also found in his study 41.8% had hepatomegaly^[19]. Kumar *et al.* noted in his study that 34 (69.3%) had hepatomegaly 20 (40.8%) had splenomegaly^[37]. Wu *et al.* noted in his study association of abdominal pain with scrub typhus in 30.9%^[1]. In the present study hepatomegaly in 18 (39.1%) patients and splenomegaly in 29 (63%) was significantly associated with severe scrub typhus. Sriwongpan *et al.* also found hepatomegaly in 36 (36%) and splenomegaly in 9 (9%) were associated with severe scrub typhus^[12]. We did

a multivariate analysis and our study established presence of hepatomegaly (odds 1.9; 95% *CI* 0.9–3.8) and splenomegaly (odds 1.1; 95% *CI* 0.8–2.4) as an independent risk factor for severe scrub typhus.

In our study we noted elevated liver enzymes with mean SGOT of (180.3±127.2) IU/L and mean SGPT of (164.1±101.2) IU/L which is approximately 4 times the normal value. Our findings were advocated by other previous studies^[12,52]. Chanta *et al.* found in his study a mean SGPT of (197.7±126.6) IU/L^[53], and Sriwongpan *et al.* also identified elevated SGPT levels as a risk factor for scrub typhus^[12]. Wu *et al.* mentioned in his study a common occurrence of hepatic dysfunction, noted in 75%–92% patients with scrub typhus^[1]. In our study there was no significant association with serum SGPT and SGOT with severe scrub typhus. However, some studies have found a significant association of SGOT and SGPT with severe scrub typhus^[13,37].

4.10. Serum albumin

In our study, we established 30 (31%) of patients had low levels of serum albumin, and low albumin levels were significantly associated with severe scrub typhus in 19 (43.1%) compared to mild scrub typhus in 11 (22%), previous studies also support our findings^[6,12,15,17]. Several researchers have reported that in scrub typhus, liver may be affected, decreasing its albumin production and this in association with leakage of albumin from blood vessels, caused by vasculitis, leaves the patients with hypoalbuminemia^[53]. However, few studies have reported contradictory findings with no association of scrub typhus infection and serum albumin levels^[14]. These findings need to be further explored in a large patient sample.

4.11. Secondary infections

In our study we found 10 patients (10.4%) had secondary infections, similar findings were reported by Mahajan *et al.* in India^[54]. Secondary infections were more common in severe scrub typhus. We also noted other risk factors for secondary infections like diabetes mellitus in 18 (18.7%), hypertension in 25 (26.0%), smoking in 15 (15.6%) and alcoholics in 10 (9.6%). Park *et al.* assessed the risk factors associated with severity of scrub typhus^[55], and identified old age and underlying chronic diseases like diabetic mellitus and other less frequent diseases as independent risk factors. This reconfirms our clinical impression that elderly patients from rural areas with underlying chronic diseases are more likely to have more severe clinical presentations, secondary infections and prolonged morbidity^[55].

4.12. Seasonal variation

In our study majority of patients 58 (60%) with scrub typhus were admitted in our hospital during the period from June to November. Our findings are advocated by other Indian

studies^[4,5,13]. Liu *et al.* noted in his study that scrub typhus cases occurred during autumn–winter period in China^[20], while others have noted a peak time of occurrence in October and November in Korea^[56]. However, some studies from Japan and South China have found a higher prevalence of scrub typhus in spring^[10]. The seasonal variation also seems to extend the disease manifestation. Zhou *et al.* from southern China found patients affected in summer time developed severe complications like toxic myocarditis, alimentary tract hemorrhage, pleural effusions, or abdominal dropsy^[57]. On the other hand Liu *et al.* observed in his study that myocarditis, pleural effusion and gastrointestinal hemorrhage were more common in winter scrub typhus^[20]. In our study, 15 (15.6%) patients with pleural effusion, 10 (10.4%) with pulmonary edema 3 (3.1%) with peribronchial infiltrate 2(2.1%) with reticular infiltration, and 1 (1%) with air–space consolidation were seen to be affected in the months of October and November. The occurrence pattern seems to correspond to the time of cultivation and exposure *e.g.*, in India, cultivation time is between June and September (monsoon time). There also seem to be seasonal and geographical variation in the species of chigger mites which has been established by Ogawa *et al.*^[10], and Hashimoto *et al.*^[58]. The difference in the species can be a reason, some clinical symptoms like lymphadenopathy, retro–orbital pain, electrocardiogram abnormality, hepatosplenomegaly, and flank tenderness seem to occur more commonly in summer than autumn–winter^[20].

4.13. Low socioeconomic status

Our study had a major proportion of patients *i.e.*, 60(62.5%) in the low socioeconomic. Several reports have found low socioeconomic group had a higher chances of getting affected with scrub typhus^[8,9,59,60]. In the present study 42(46.8%) patients were farmers and working in the fields. Our finding were advocated by Ogawa *et al.*, he found in his study 44% of patients were engaged in farming^[10]. Similar findings were established by Wardrop *et al.*^[59]. Sharma *et al.* noted in his study that farmers working in bushes, piles of wood with domestic animals and rodents were significantly more affected with scrub typhus^[61]. Few patients in our study were daily agricultural workers and were staying in the edge of their villages. Lyu *et al.* also noted in his study that most of the affected scrub typhus patients, living at the edge of the village, were nearer to the farmland or grassland, where the chigger mite grows, and thus more likely to have contact with the transmission vectors of scrub typhus^[8]. Also the clothing pattern with farmers working with their upper trunk uncovered may increase their risk of catching the disease.

4.14. Mortality

The present study demonstrated a mortality rate of 2% and both the patients who died had severe scrub typhus. Similar reports were noted with the death of one patient in a series

from South Korea^[45]. Kumar *et al.* established mortality rate in untreated scrub typhus patients from 0%–30% due to the rickettsial strain, intervention time and geographic area^[7]. Our present data showed the mortality rate to be lower than other studies, 6.1% in a study by Lee *et al.*^[17], 12.2% in a study by Chrispal *et al.*^[62], and 33.5% in a study by Narvencar *et al.*^[6]. Recent reports have established serious complications with scrub typhus and a mortality rate of 7%–43%^[63–65]. Scrub typhus can be a life threatening disease, the severity of the disease and mortality is increased by noneschar forming variant, delayed diagnosis^[17], and delayed treatment^[66]. Mahajan established in the three factors– late presentation, delayed diagnosis and drug resistance as causes of mortality^[67].

In our study one of the deceased had severe scrub typhus with hematological complication and the other had renal failure and cardiac disease. Vagrhesse *et al.* found an elevated serum creatinine level as an independent predictor for mortality in scrub typhus patients^[64].

4.15. Therapeutic

Out patients started treatment by the 3rd day after admission after confirming the results by Weil Felix or ICT along with eschars.

Scrub typhus is prevalent all over India. Our study showed significant association of cough, eschar, hepatomegaly, poor GCS, cough and meningoencephalitis, with severe scrub typhus. In India scrub typhus affects farmers commonly, who work in the fields and have a low socioeconomic status. Monsoon time from June to September is the period, most cases are admitted in our hospital. Our study observed CSF protein levels were elevated and sugar levels reduced commonly suggesting meningitis. Our study mortality rate was low and possibly because our patients attended the hospital early and with our high degree of suspicion, we could diagnose the disease early. The confirmation of scrub typhus by the two serological examinations, Weil Felix and the ICT is obtained early too. Thus lead to a rapid initiation of treatment within 3 days of admission. Although in this study we present cases with clear diagnosis, it is advisable to empirically start doxycycline in suspected cases of scrub typhus. Doxycycline can be life saving and an absence of eschar and a negative Weil Felix test should not exclude the diagnosis as their sensitivities are low. A larger scale study is required to confirm these findings.

Conflict of interest statement

We declare that we have no conflict of interest.

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