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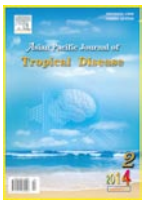

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Predictors of severity of scrub typhus in the Indian subcontinent

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ABSTRACT

Objective: To identify the factors for predicting severity in scrub typhus which is an acute febrile illness caused by *Orientia tsutsugamushi*.

Methods: A prospective study of 220 patients with scrub typhus was conducted at Kasturba hospital during May 2012 to April 2013, out of which 116 patients were in the severe disease group and 104 in the non-severe group.

Results: Using univariate analysis, the presence of the following factors, namely age>40 years, haemoglobin<12 g/L, white blood cell count>10 000 cells/mm^3, platelet<150 000 cells/mm^3, albumin<3.5 g/dL and the absence of eschar were correlated with severe disease. However, on multivariate analysis, haemoglobin<12 g/dL (OR=2; *P*=0.037; *CI*=1.04-3.82); white blood cell count>10 000 cells/mm^3 (OR=3; *P*=0.001; *CI*=1.5-5.8), platelet<150 000 cell/mm^3 (OR=6.2; *P*<0.001; *CI*=3.1-12.4) and absence of eschar (OR=0.4; *P*=0.01; *CI*=0.2-0.8) were found to be predictors of severity.

Conclusions: We conclude haemoglobin<12 g/dL, WBC count>10 000/mm^3, platelet<150 000/mm^3 and absence of eschar to be independent predictors of severity of illness in scrub typhus.

1. Introduction

Scrub typhus is an acute febrile illness caused by (*O. tsutsugamushi*) and is endemic over Eastern Asia, the Indian subcontinent and Southern Pacific[1,2]. It is characterised by high grade fever, maculopapular rash, lymphadenopathy, myalgia and eschar. It is produced by the bite of the trombiculid mite, the natural host, which inoculates humans (accidental hosts) in its infected larval stage[1,3]. Typical feeding locations are the sites where the clothes bind for example the groin, axilla and inguinal regions[3]. Scrub typhus can range from a mild disease with a self-limiting course, to a severe disease with a protracted course leading to mortality in untreated cases[1]. Severe complications include meningoencephalitis, myocarditis, pneumonia, septic shock and renal failure[4,5].

It has been reported that approximately one billion people are at risk of infection with one million new cases of scrub typhus being reported per year[3]. The recent resurgence of cases in India is probably due to under-diagnosis or misdiagnosed of cases in the past. Untreated, the mortality can range from 14%to 30% in Southeast Asia[6]. Scrub typhus has now emerged as a significant cause of zoonosis of importance to public health[7]. There is paucity in data regarding the factors that predict severity in scrub typhus. Our study aimed to identify such risk factors that would predict a severe outcome in scrub typhus so as to facilitate prompt and aggressive therapy.

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2. Materials and methods

2.1. Study location

This study was conducted at Kasturba Hospital, Manipal which is a 2500 bedded tertiary health care centre located in Southern India. Informed consent was obtained from all patients participating in the study. Ethical clearance was obtained from institutional review board.

2.2. Selection criteria of study population

A prospective study of 255 consecutive patients who were admitted with scrub typhus over one year period between May 2012 to April 2013 were included in the study. Patients above 18 years with acute febrile illness with eschar or maculopapular rash or possibility of scrub typhus were included. Definitive diagnosis was obtained by positive ELISA for scrub IgM or using indirect immunofluorescent antibody assay (IFA) IgM titer against *O. tsutsugamushi*. IFA titres of ⩾1:80 or four fold or more rise in titres was considered diagnostic for scrub typhus[1]. The demographics, clinical presentation, distribution of eschar and length of hospital stay were noted along with mean duration from disease onset to initiation of effective antibiotics for both the groups. The various laboratory parameters comprising of a baseline complete blood investigations with renal and liver function tests performed at the time of admission were noted. Co-infections with leptospirosis, dengue, enteric fever and malaria were ruled out with the appropriate investigations.

2.3. Definitions

Severe disease was defined as the presence of any one of the following: (1) acute renal failure with creatinine levels >1.6 g/dL or at least 50% reduction in glomerular filtration rate using the modified diet in renal disease equation: glomerular filtration rate (mL/min/1.73 m^2)=175×SerumCr-1.154×age-0.203×1.212 (if patient is black)×0.742 (if female); (2) presence of pneumonia was diagnosed by symptoms of cough with expectoration with parenchymal changes on chest roentogenography; (3) presence of shock which is defined by arterial blood pressure of <90 mmHg systolic or 40 mmHg less than normal systolic blood pressure (120 mmHg) despite adequate fluid resuscitation for 1 h; (4) central nervous system involvement in the form of meningoencephalitis diagnosed clinically by presence of either headache, altered sensorium, seizures or coma with a cell count of >5 cell/mm^3 on cerebrospinal fluid analysis; (5) myocarditis.

2.4. Statistical analysis

Categorical data was expressed using frequencies and the differences between two study groups were compared using *Chi*-square test. Continuous data was expressed using median and interquartile range with comparison of data between the 2 groups using independent *t*-test or Mann-Whitney test. Univariate logistic regression and *Chi*-square test were used to determine the association between the variables and severity of disease. A multivariate analysis using step wise multiple logistic regression was then performed using the variables found to be significant ($P<0.2$) by univariate analysis to predict severity of scrub typhus. The data was expressed as unadjusted and adjusted odds ratio (OR) with a 95% confidence interval (*CI*). A *P*-value of less than 0.05 was considered statistically significant. SPSS version 20 was used for data analysis.

3. Results

Out of 255 patients recruited, 10 patients succumbed to complications, 13 patients suffered from co-infection with leptospirosis, 8 were discharged before completion of therapy and 4 patients didn't consent to the study, and they were excluded from the study (Figure 1). A total of 220 patients who met the inclusion criteria were divided into 2 groups, non-severe (n=104) and severe group (n=116) based on the criteria for severity of disease. Amongst the patients in severe group, 40 patients (34.5%) had pneumonia, 26 patients (22.4%) had meningoencephalitis, 44 patients (37.9%) were in renal failure, 26 patients (22.4%) were in shock and 2 patients (1.7%) suffered from myocarditis.

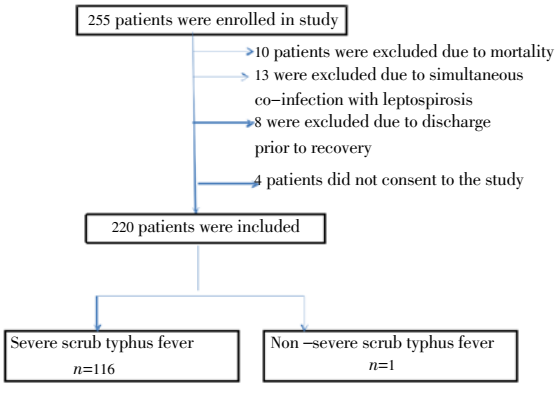

Figure 1. Patients enrolled in the study.

Table 1 summarizes the demographic and clinical features of both the groups. The mean age of presentation in the severe group was (39.20±15.04) years which was higher as compared to the non-severe group (36.70±11.50) years. There was a significant male preponderance of cases in the non severe group (n=78) as compared to the severe group (n=66). There was no significant difference between the duration of illness prior to hospitalisation amongst both groups. Length of hospital stay was significantly longer in the severe group 9.5 days with interquartile range [IQR (8, 12)] as compared to 5 days [IQR (7, 9)] in non-severe group (Table 1). The distribution of clinical features like fever, maculopapular rash, headache, abdominal pain, vomiting and myalgia were similar between both the groups as seen in Table 1. Eschar was more commonly found in the non-severe group (40.4%) as compared to the severe group (18.9%). The other clinical and demographic variables are as depicted in Table 1. A significant disparity in haemoglobin, total white blood cell count (WBC), prothrombin time, total bilirubin and albumin was observed between the two groups as summarized in Table 2.

Table 1
Demographic and clinical features of patients with scrub typhus fever at admission.

Characteristics		Severe scrub typhus (n=116)	Non-severe scrub typhus (n=104)	P-value
Demographics	Age >40 years	48 (37.1%)	42 (40.3%)	0.88
	Males	66 (56.9%)	78 (75%)	0.004
	Females	50 (43.1%)	26 (25%)	0.02
Duration of disease to initiation of effective antibiotics (mean±SD)		7±4.2	6.4±3.11	0.1
Length of hospital stay (days)		9.5 (8, 12)	5.0 (7, 9)	0.002
Clinical features	Fever	116 (100.0%)	102 (98.1%)	0.22
	Headache	46 (39.7%)	46 (44.2%)	0.13
	Eschar	22 (18.9%)	42 (40.4%)	<0.001
	Maculopapular rash	5 (4.3%)	6 (5.8%)	0.18
	Arthralgia	8 (6.9%)	14 (13.5%)	0.08
	Myalgia	36 (31.0%)	25 (24.0%)	0.16
	Cough	39 (33.6%)	25 (24%)	0.061
	Breathlessness	44 (37.9%)	8 (7.7%)	0.000
	Abdominal pain	28 (24.1%)	32 (30.8%)	0.17
	Jaundice	18 (15.5%)	9 (8.7%)	0.09
	Vomiting	34 (29.3%)	31 (29.9%)	0.53
	Altered sensorium	6 (5.2%)	3 (2.9%)	0.003
	Oliguria	22 (19%)	6 (5.8%)	<0.001
	Loose stools	4 (3.4%)	4 (3.8%)	0.57
	Hematemesis	4 (3.4%)	0	0.65
	Hepatomegaly	50 (43.1%)	36 (34.6%)	0.125
	Spleenomegaly	34 (29.3%)	21 (20.2%)	0.01
	Lymphadenopathy	40 (34.5%)	22 (21.2%)	0.001

Using univariate analysis (Table 3), four variables, namely age >40 years (OR=1.04; CI=0.61-1.80; P=0.88), haemoglobin <12 g/dL (OR=2.27; CI=1.30-4.00; P=0.004), WBC count >10 000 cells/mm^3 (OR=0.4; CI=0.23-0.73; P=0.002) and platelet <150 000 cells/mm^3 (OR=6.5; CI=3.40-12.50; P<0.001) correlated with severity of scrub typhus. The presence of an eschar correlated with less severe disease (OR=0.345; CI=0.18-0.63; P=0.001). We excluded creatinine for analysis as it was included as a part of the definition for severe disease. Multivariate analysis as shown in Table 4, revealed haemoglobin <12 g/dL (OR=2.0; P=0.037; CI=1.04-3.82), WBC >10 000 cells/mm^3 (OR=3.0; P=0.001; CI=1.50-5.80), platelet <150 000 cell/mm^3 (OR=6.2; P<0.001; CI=3.10-12.40) and absence of eschar (OR=0.4; P=0.01; CI=0.2-0.8) to be predictors of severity.

Table 2
Distribution of laboratory characteristics according to disease severity. Median (IQR).

Laboratory findings	Severe disease	Non-severe disease	P-value
Haemoglobin (g/dL)	12 (10.0, 13.0)	13 (11.6, 14.0)	<0.001
WBC count (cells/mm^3)	9.40 (7.08, 14.48)	8.10 (6.20, 10.00)	0.001
ESR (mm/hr)	44 (26, 64)	34 (19, 52)	0.104
PT (seconds)	17.0 (16.0, 19.4)	16.0 (14.0, 17.0)	0.003
Total bilirubin (mg/dL)	2.0 (1.0, 4.0)	0.9 (0.3, 2.1)	<0.001
AST (IU/L)	113.0 (63.0, 191.0)	94.0 (51.0, 134.5)	0.032
ALT (IU/L)	79 (53, 120)	87 (62, 122)	0.13
ALP (U/L)	203 (150, 295)	172 (96, 328)	0.17
Albumin (g/dL)	2.7 (2.5, 3.0)	3 (2.9, 3.4)	0.03
Total protein (g/dL)	6.00 (5.00, 6.13)	6.50 (6.00, 7.00)	<0.001
Serum creatinine (mg/dL)	1.00 (0.92, 2.00)	1.00 (0.90, 1.00)	<0.001
Amylase (IU/L)	73.5 (44.0, 182.0)	70.0 (46.0, 87.0)	0.27
Lipase (IU/L)	39.0 (20.0, 116.0)	29.0 (17.5, 40.0)	0.13

IQR: Interquartile range; WBC: White blood cell; ESR: Erythrocyte sedimentation rate; PT: Prothrombin time; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase.

Table 3
Unadjusted OR for factors associated with severe scrub typhus fever.

Characteristis	Severe disease (n=104)	Non severe scrub disease (n=116)	OR	CI	P-value
Age >40 years	48 (41.40%)	42 (40.40%)	1.040	0.61-1.80	0.88
Eschar	22 (18.96%)	42 (40.38%)	0.345	0.18-0.63	0.001
Hemoglobin (<12 gm/dL)	55 (47.40%)	29 (27.90%)	2.270	1.30-4.00	0.004
WBC count (>10 000/mm^3)	52 (44.80%)	26 (25.00%)	0.400	0.23-0.73	0.002
Platelet (<150 000/mm^3)	100 (86.20%)	51 (49.00%)	6.500	3.40-12.50	<0.001

Table 4
Unadjusted and adjusted OR for severe scrub typhus provided by step wise multiple logistic regression.

Characteristics	Unadjusted OR		Adjusted OR		P-value
	OR	CI	OR	CI	
Haemoglobin (< 12 g/dL)	2.27	1.30-4.00	2.0	1.04-3.82	0.037
WBC count (>10 000 mm^3)	0.40	0.23-0.73	3.0	1.50-5.80	0.001
Platelet count (<150 000 mm^3)	6.50	3.40-12.50	6.2	3.10-12.40	<0.001
Eschar	0.35	0.18-0.63	0.4	0.20-0.80	0.01

4. Discussion

With the recent resurgence of cases and scrub typhus being a treatable disease, it becomes pertinent to identify the factors that lead to severity. Epidemiological trends suggest increased incidence of disease post rains, due to an increased vegetation which supports larval growth of the trombiculid mite[8,9]. Serious complications are not uncommon. Thus early diagnosis and timely institution of antibiotic therapy remains the key to prevent complications. Weil-Felix test has high specificity but a low sensitivity to diagnose scrub typhus. However it continues to be used as it is the cheapest available test for diagnosis. Positive Weil-Felix test is defined as single serum sample titres of >1:320 or a 4 fold rise in titres in paired sera[5]. However, IFA is considered as the gold standard diagnostic tool in scrub typhus, along with PCR based assays[10,11]. The current antibiotic trend for scrub typhus includes cephalosporins, extended spectrum penicillins and flouroquinolones[8,9]. Only cases that fulfilled the definition of severe disease were studied. Severe scrub typhus leading to mortality varied from 15%-30% in a study by Watt G and 14% as reported by Verghese *et al.* in the Indian subcontinent[3,12].

The mean age of presentation was (39.20±15.04) years in the severe group and (36.70±11.50) years in the non-severe group with no significant difference. This corresponds to the age group actively involved in recreational or occupational activities, subjecting them to risk of the disease. In a study done by Verghese *et al.*[12], median age of scrub typhus patients in the southern part of India was 36.5 years (range: 12-75 years). On univariate analysis taking age >40 years as a risk factor for severity, we found no statistical significance between the 2 groups. This is as opposed to the study done by Kim *et al.* who found that age >60 years was a predictor of severity[13].

Presence of eschar is a significant clinical finding as it helps in early diagnosis by clinicians followed by prompt therapy. It is easily identifiable in Caucasians and East Asian patients as compared to the dark-skinned Indians occurring in <10% of Indian population[6,7]. The cause for this is not very clearly defined. It represents the site of feeding of the chiggers and begins as a papule, undergoing central necrosis and later crust formation. In a study done by Park *et al.*, the eschar was used to extract DNA template for genotyping of *O. tsutsugamushi*[12,14]. We didn't perform genotyping due to its non-availability in our setting. In our study, we observed the presence of eschar to be significantly higher in the non-severe group (40.38%) as opposed to the severe group (18.96%)[15,16]. We also observed the absence of eschar to be an independent variable to predict severe scrub typhus (adjusted OR=0.4) by multivariate analysis, which is in agreement to the study done by Kim *et al.*[13]. Thus, the presence of eschar could be viewed as a good sign. Even in the absence of eschar, clinicians must keep the diagnosis of scrub typhus in mind.

We did not observe a significant difference in the duration between appearances of symptoms to initiation of antibiotic therapy among both the groups. Assuming that people with an eschar would seek medical assistance earlier, we expected to find a shorter delay in hospitalisation in such patients which however did not occur. The duration of hospital stay was significantly higher in the severe group [9.5 days, IQR (8,12)] as compared to the non-severe group [5 days, IQR (7,9)] (P=0.002).

The severity of disease in scrub typhus is probably due to obligate intracellular nature of *O. tsutsugamushi* which rapidly divides in the endothelium of blood vessels[17]. It gets disseminated to various organs in the body like the heart, kidney, liver and brain[18]. A number of immune cytokines like tumor necrosis factor-alpha are released during the acute phase and these levels are said to positively correlate with severity of disease[19]. The WBC count was found to be significantly higher for the patients in the severe scrub typhus group. Multivariate analysis revealed WBC count >10 000 mm^3 to be an independent risk factor for predicting severity (OR=3.0; CI=1.50-5.80; P=0.001). Studies done by Lee *et al.*[16] and Kim *et al.*[13] also found WBC count to be higher in the severe group which suggested a more serious infection with severe inflammation.

In our study, we failed to demonstrate hypoalbuminemia as an independent risk factor of severity. Hypoalbuminemia is probably due to extravascular leakage of proteins which is due to the increased vascular permeability of the damaged endothelial cells as a consequence to disseminated vasculitic process affecting the small blood vessels[20,21]. Kim *et al.* found an albumin level <3 g/dL to be a predictor of severity of disease[13]. Lee *et al.* found hypoalbuminemia to correlate with more complications and longer hospital stay[22]. In our study, both groups of patients showed more or less similar trends of albumin levels. Hence, we didn't observe a significant difference between both groups.

We observed anemia (haemoglobin <12 g/dL) to be a predictor of severe illness (OR=2; CI=1.04-3.82; P=0.03).

The study by Kim *et al*., however failed to demonstrate haemoglobin <12 g/dL as a significant predictor of severity on multivariate analysis, though there was a significant difference seen after univariate analysis.

In conclusion, haemoglobin <12 g/dL, WBC count >10 000/mm^3, platelet <150 000/mm^3 and absence of eschar were independent predictors of severity of illness in scrub typhus. These indicators will facilitate clinicians to identify patients who are at risk of developing severe illness, thus prompting an early and more aggressive therapy. Clinicians must have a high index of suspicion of scrub typhus even in absence of an eschar.

Conflict of interest statement

We declare that we have no conflict of interest.

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