

ORIGINAL ARTICLE

Predictors of Severity in Scrub Typhus

Ritin Sharma¹, Sanjay K Mahajan^{2*}, Balraj Singh³, Rajiv Raina⁴, Anil Kanga⁵**Abstract**

Aims: To study predictors of severity in patients of scrub typhus admitted in a tertiary care hospital.

Material and Methods: Total 92 patients of scrub typhus were included in the study. The diagnosis was established by presence of IgM antibodies by Indirect Immunofluorescence Assay (IFA) test which is currently the reference standard for the diagnosis of scrub typhus. The clinical and laboratory profile, course in hospital, and outcome were documented. Factors associated with severe disease were analyzed.

Observations: Fever (100%), cough (37%), headache (33%), vomiting (31%), altered sensorium (23%), diarrhea (18%), abdominal pain (16%), myalgia (14%), and seizures (3%) were common clinical features. An eschar was present in 23% of patients. Common laboratory findings included elevated transaminases (61%), thrombocytopenia (39%), and leukocytosis (30%). Severe sepsis was present in 33% patients. Septic shock was present in 4% patients. Presence of one or more organ failure was seen in 34% of patients. The overall case-fatality rate was 4%. Factors significantly associated with organ failure (severe disease) were leukocytosis ($p < 0.001$), hyperbilirubinemia ($p < 0.001$), high SGOT levels ($p 0.030$), hypoalbuminemia ($p < 0.001$), high urea levels ($p < 0.001$), and high creatinine levels ($p 0.012$). Among the criteria used to classify severity of scrub typhus, presence of one or more organ failure was significantly associated with mortality ($p 0.004$).

Conclusion: Scrub typhus can manifest with potentially life-threatening complications such as meningoencephalitis, septic shock, ARDS, acute liver failure, acute kidney injury, severe thrombocytopenia. Leukocytosis, hyperbilirubinemia, transaminitis, hypoalbuminemia, and uremia were associated with organ failure and were significantly associated with morbidity and mortality.

Introduction

Orientia tsutsugamushi and Rickettsia species are important cause of non-malarial febrile illness in Southeast Asia preceded only by dengue.¹ Among rickettsioses, scrub typhus is most common followed by Indian tick typhus.² The incubation period for symptoms ranges between 6 to 21 days from exposure. Patients may present with sudden fever, chills, headache, backache, profuse sweating, vomiting and enlarged lymph nodes. A macular or maculopapular rash may appear on the trunk, and later it may extend to the arms and the legs. An eschar at the wound site is the single most useful diagnostic clue.³ The Indirect Immunofluorescence Assay (IFA) test is currently the reference standard for

the diagnosis of scrub typhus.⁴

Treatment with doxycycline is associated with a rapid abatement of fever and this effect has even been considered almost diagnostic. Azithromycin is also effective and is easier to administer, given its shorter treatment duration, and less gastrointestinal side effects. It is suitable for use in pregnancy and for children.⁵

The symptoms of scrub typhus are usually mild and its clinical course is uneventful. However, some patients

experience severe or fatal events. Serious complications include pneumonitis, acute respiratory distress syndrome, acute renal failure, myocarditis, and septic shock. Mortality rates in untreated patients range from 0-30%.⁶

In the studies of scrub typhus in Indian Literature, the diagnosis is based on Weil Felix test or IgM ELISA. In present study the diagnosis of scrub typhus was done by Indirect Immunofluorescence Assay (IFA) test which is currently the reference standard for the diagnosis of scrub typhus however the test is expensive and requires considerable training.⁴

Methods

The study was conducted among all adult (age ≥ 18 yrs.) patients of scrub typhus admitted to wards of a tertiary care hospital from July 1st 2015 through June 30th 2016.

Inclusion Criteria

1. Patients diagnosed as Scrub typhus with IFA.
2. Age ≥ 18 years.

Exclusion Criteria

Patients of scrub typhus with co-infections and pregnant patients were not included.

Operational Definitions**Scrub typhus**

A patient showing clinical features consistent with scrub typhus and IgM antibodies by IFA

Severe Disease

A case of scrub typhus with criteria fulfilling severe sepsis or septic shock or evidence of organ system failure was defined as severe disease and a case of scrub typhus leading to mortality was defined as a poor outcome.

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Table 1: Clinical characteristics among study participants by gender.

Symptoms and signs	All participants (n=92)		Men (n=26)		Women (n=66)		p-value*
	No.	%	No.	%	No.	%	
High grade fever ($\geq 102^{\circ}\text{F}$)	25	27.2	7	26.9	18	27.3	0.973
Chills/Rigors	73	79.3	23	88.5	50	75.8	0.175
Duration of presenting complaint							
<7 days	29	31.5	7	26.9	22	33.3	0.523
7 – 14 days	52	56.5	17	65.4	35	53.0	
>14 days	11	12.0	2	7.7	9	13.6	
Cough	34	37.0	9	34.6	25	37.9	0.770
Headache	30	32.6	11	42.3	19	28.8	0.213
Vomiting	29	31.5	7	26.9	22	33.3	0.551
Altered sensorium	21	22.8	8	30.8	13	19.7	0.255
Eschar	21	22.8	4	15.4	17	25.8	0.286
Diarrhoea	17	18.5	4	15.4	13	19.7	0.439
Abdominal Pain	15	16.3	5	19.2	10	15.2	0.423
Jaundice	15	16.3	5	19.2	10	15.2	0.423
Myalgia	13	14.5	3	11.5	10	15.2	0.654
Rash	6	6.5	6	23.1	0	0.0	<0.001
Seizures	3	3.3	1	3.8	2	3.0	0.636
Lymphadenopathy	13	14.1	4	15.4	9	13.6	0.531
Organomegaly							
Splenomegaly	3	3.3	1	3.8	2	3.0	1.000
Hepatomegaly	6	6.5	2	7.7	4	6.1	1.000
Hepato-splenomegaly	4	4.3	2	7.7	2	3.0	0.316
Ascites	2	2.2	0	0.0	2	3.0	1.000
Tenderness epigastrium	1	1.1	1	3.8	0	0.0	0.283
Crepitations	28	30.4	9	34.6	19	28.8	0.584
Pallor	13	14.1	1	3.8	12	18.2	0.066

*P-value calculated by chi-square test or Fisher's exact test as admissible based on the data distribution.

Table 4: Outcomes of patients by severity of disease (SIRS, Severe Sepsis/Septic shock, organ failure)

Severity criteria	N	ICU admission			Death				
		No.	RR ¹⁰	95% CI ¹¹	p-value	No.	RR	95% CI	p-value
SIRS									
With SIRS	70	8	Undefined	Undefined	0.097	3	0.9	0.1-8.6	0.958
Without SIRS	22	0				1			
Severe Sepsis									
Present	30	4	2.1	0.6-7.7	0.272	2	2.1	0.3-14.0	0.448
Absent	62	4				2			
Organ system failure									
Present	31	5	3.3	0.8-12.8	0.071	4	Undefined	Undefined	0.004
Absent	61	3				0			
Severe Disease ¹²									
Present	46	6	3.0	0.6-14.1	0.139	4	Undefined	Undefined	0.041
Absent	46	2				0			

¹⁰Relative risk; ¹¹Confidence interval; ¹²Severity by either criteria

Severe sepsis

The harmful host response to infection, systemic response to proven or suspected infection, plus some degree of organ hypofunction i.e.

1. Cardiovascular: Arterial systolic blood pressure ≤ 90 mm Hg or mean arterial pressure ≤ 70 mm Hg that responds to administration of IV fluids.

2. Renal: Urine output < 0.5 ml/kg per hour for 1 hour despite adequate fluid resuscitation.
3. Respiratory: $\text{Pao}_2/\text{Fio}_2 \leq 250$ or, if lung is the only dysfunctional organ, ≤ 200 .
4. Hematologic: Platelet count $< 80,000/\mu\text{l}$ or 50% decrease in platelet count from highest value recorded over previous 3 days.

Table 3: Distribution of patients by severity of disease (SIRS, Severe Sepsis/Septic shock, organ failure)

Severity criteria	All participants (n=92)		Men (n=26)		Women (n=66)		p-value ²
	No.	%	No.	%	No.	%	
Sepsis							
SIRS ³	70	76.1	26	100.0	44	66.7	0.001
Severe Sepsis ⁴	30	32.6	13	50.0	17	25.8	0.026
Septic Shock	4	4.3	2	7.7	2	3.0	0.316
Organ system failure							
Renal							
BUN > 100 mg/dL	2	2.2	0	0.0	2	3.0	0.512
Creatinine > 3.5 mg/dL	8	8.7	1	3.8	7	10.6	0.279
Hepatic ⁵	6	6.5	1	3.8	5	7.6	0.453
Neurologic ⁶	21	22.8	8	30.8	13	19.7	0.255
Haematologic ⁷	2	2.2	0	0.0	2	3.0	0.512
Anyone of above ⁸	31	33.7	10	38.5	21	31.8	0.544
MODS ⁹	5	5.4	0	0.0	5	7.6	0.182

²p-value calculated by chi-square test or Fisher's exact test as admissible based on the data distribution; ³SIRS: Severe Inflammatory Response Syndrome; ⁴SIRS with any one or more of the Severe Sepsis components; ⁵Serum bilirubin > 6.0 mg/dl; ⁶Altered sensorium; ⁷Platelet count $< 20,000/\mu\text{l}$; ⁸Organ system failure; ⁹Two or more organ system failure

Table 2: Comparison of haematologic and biochemical findings by organ failure and without organ failure

	Organ failure (n=31)		No organ failure (n=61)		P-value ¹
	Mean	S.D.	Mean	S.D.	
Hematologic					
Hemoglobin	10.8	1.4	11.8	2.2	0.021
TLC (thou/ μl)	13.7	6.1	8.7	4.6	<0.001
Platelets (thou/ μl)	94.3	101.4	126.8	77.8	0.091
Biochemical Profile					
Bilirubin	4.0	5.1	1.3	1.2	<0.001
SGOT	472.0	1506	161.0	191.0	0.030
SGPT	251.9	754.4	120.9	184.6	0.340
ALP	269.8	173.9	205.8	217.6	0.159
Serum protein (g/dl)	5.3	0.9	6.2	0.8	<0.001
Serum albumin (g/dl)	2.4	0.6	3.1	0.6	<0.001
Urea	73.3	54.1	36.2	23.2	<0.001
Creatinine	2.2	2.6	1.1	0.7	0.012
Sodium	135.2	8.5	137.6	5.0	0.268
Potassium	3.6	0.6	3.9	0.5	0.017
Cholesterol	128.0	45.4	129.3	35.9	0.880
HDL	25.9	17.2	29.3	13.3	0.289
RBG	120.8	56.05	107.3	28.4	0.467

¹p-value calculated by chi-square test or Fisher's exact test as admissible based on the data distribution.

5. Unexplained metabolic acidosis: pH ≤ 7.30 or base deficit ≥ 5.0 mEq/L and plasma lactate level > 1.5 times upper limit of normal.

Septic shock

Defined as Sepsis with hypotension (arterial blood pressure < 90 mm Hg systolic) for at least 1 hour despite adequate fluid resuscitation.

Or

Need for vasopressors to maintain systolic blood pressure ≥ 90 mm Hg or mean arterial pressure ≥ 70 mm Hg.⁷

Organ system failure

Neurologic: Glasgow Coma Score < 6 (in absence of sedation)

Cardiovascular:

- Heart rate < 54 beats per min
- Mean arterial blood pressure < 49 mm Hg (systolic blood pressure < 60 mm Hg)
- Ventricular tachycardia, ventricular fibrillation, or both

Pulmonary:

- PaCO₂ > 50 mm Hg (acutely)
- Ventilator or continuous positive airway pressure dependence on the second day of organ dysfunction

Hepatic:

- Jaundice (bilirubin > 6 mg/100 dL)
- Coagulopathy (Prothrombin Time, 4 sec greater than control, in the absence of anticoagulation)

Renal:

- Urine output < 479 mL/24 hr or < 159 mL/8 hr
- Serum BUN > 100 mg/100 dL
- Serum creatinine > 3.5 mg/100 dL

Hematologic:

- White blood count < 1, 000 cells/mm³
- Platelets < 20, 000 platelets/mm³
- Hematocrit < 20%.⁸

A brief history regarding presenting complaints, relevant past history, and personal history was recorded. Patients were subjected to general and systemic examination. Hematological and biochemical investigations were done as a part of fever workup. Patients were subjected to imaging studies where indicated.

IgM Indirect Immunofluorescence Assay (IFA)

An IFA for the detection and semi quantitative determination of IgM class antibody against *Orientia tsutsugamushi* in human serum or plasma was done using kit manufactured by Fuller Laboratories.

Data was collected from time of admission to discharge / death. We entered data on Microsoft excel spreadsheet and was analyzed using Epi Info 7.1.5 for windows. We did descriptive analysis for baseline characteristics of patients.

The study was cleared by Institutional Ethics Committee.

Results

Total 92 admitted patients of scrub typhus aged from 18 years to 80 years were included in the study. Seventy eight (85%) patients were in age group of 18-60 years. Out of 92 patients, 72% were females and 28% were males with the ratio of female to male 2.5:1. Fever was present in all cases, however high grade fever was present in 27% patients. The clinical details of patients are given in Table 1.

The comparison of hematologic and biochemical findings in patients with organ failure and without organ failure is given in Table 2.

Among hematological findings, there was significant difference in mean hemoglobin (p 0.021) and mean leucocyte count (p < 0.001) in patients with organ failure and without organ failure. Among biochemical abnormalities, hyperbilirubinemia (p < 0.001), mean SGOT (p 0.030), mean serum albumin (p < 0.001), mean serum creatinine (p 0.012) were significantly different among patients in organ failure group and in patients without organ failure.

The distribution of patients by severity of disease i.e. SIRS, Severe Sepsis/Septic shock and organ failure is given in Table 3.

SIRS was present in 76% of patients and severe sepsis was present in 33% patients, 26% were females and 50% were males. Out of components of severe sepsis thrombocytopenia was present in 37%, hypotension in 21%, acute lung injury was noted in 4% patients.

Septic shock was present in 4% patients, 8% were males, and 3% were females. SIRS, severe sepsis, septic shock all were more common in male patients.

The Organ failure (defined as dysfunction of any of organs) was present in 34% patients, and was common in males. MODS was (two or more organ failure) was present in 5% patients and all were females.

The outcomes of patients by severity of disease i.e. SIRS, Severe Sepsis/Septic shock, organ failure is given in Table 4.

When Severe Sepsis criteria were applied, there were 4 ICU admissions in both severe sepsis and non-severe sepsis group (RR=2.1, 95% CI=0.6-

7.7). In non-severe sepsis group ICU admissions were due to ventilator support required in patients due to poor GCS. There were 2 deaths in each group (RR=2.1, 95% CI=0.3-14.0).

When organ system failure criteria were applied, there were 5 ICU admissions in patients with organ failure group and 3 in patients without organ failure group (RR=3.3, 95% CI=0.8-12.8). All 4 deaths were in patients with organ failure (RR=Undefined, 95% CI=Undefined). Among the criteria used to define severity, evidence of organ failure was most significantly associated with ICU admission (p=0.071) and mortality (p=0.004).

Discussion

Scrub typhus is a febrile disease that is endemic in Asian-Pacific areas, including the Korean Peninsula. It is a clinically important disease because of its high incidence in areas of endemicity and associated with many serious complications.⁹

In our study 85% of patients were in age group of 18 to 60 years, people of this age group are mostly involved in agricultural activities or visit the forest/grass fields to collect grass for feeding their cattle. About half (49%) of patients in our study were in the age group of 21-40 years, Sharma *et al* reported highest incidence of scrub typhus in the age group of 30-40 years.¹⁰ The higher incidence in female may be due to the fact that females in this region actively participate in the agricultural or horticultural work. The typical working position of females in a squatting position, with bare hands in the fields or cutting grass predisposes them for exposure to infected mites which inhabiting soil and scrub vegetation. Mahajan *et al* in their study noted that more than 2/3rd of patients were female.¹¹

In this study, duration of symptoms at presentation was 7-14 days in 56% of patients, <7 days in 31.5% patients, >14 days in 12.0% of patients. Our State is a hilly state and majority of patients present late to a healthcare facility, leading to emergence of complications and poor outcome. The distribution of various clinical features of scrub typhus in our study were similar to a study by Tsay *et al*.¹² Eschar was present in 23% patients in our study and was lesser than other studies. This may be

due to reason that eschar is seen less frequently in South Asians, especially those who are dark skinned.¹³

The target cells for *O. tsutsugamushi* are endothelial cells and macrophages. It disseminates into the multiple organs through endothelial cells via hematogenous and lymphogenous routes and predominantly locates in the macrophages of the liver and spleen.¹⁴ Disseminated vasculitis with perivasculitis is the hallmark of scrub typhus, and involvement of the brain and lungs are the most important factors in any fatal outcome.¹⁵

Complications of scrub typhus, defined as severe disease were septic shock, renal dysfunction, altered sensorium, jaundice, thrombocytopenia, myocarditis and death. Among hematological parameters anemia, leukocytosis and thrombocytopenia were associated with severe disease. Raised SGOT levels were associated with organ failure. Mean albumin level was low in patients with organ failure. Lee *et al* concluded that hypoalbuminemia in scrub typhus was closely related to the frequency of various complications.¹⁶

Raised serum creatinine was associated with organ failure. The pathophysiology of acute renal failure is associated with prerenal azotemia due to renal hypoperfusion in cases of shock or volume depletion. Hypoalbuminemia is common with rickettsial diseases and is reported to be due to the leakage of plasma albumin into the perivascular space because of widespread vascular damage. Second, disseminated intravascular coagulation is considered another pathophysiological trait of renal failure. Third, acute tubular necrosis might cause renal failure because of the direct invasion of *O. tsutsugamushi* into a renal parenchyma.¹⁷ Mahajan *et al* reported renal dysfunction as a significant mortality risk factor.¹¹ In Table 2 urea to creatinine ratio (mean) in our study was 33.3 in patients with organ failure suggesting that intrinsic renal disease was main pathogenic process for renal dysfunction. In Table 4, organ failure was significantly associated with mortality, however combining severe sepsis and an organ failure criterion

to define severity allows detecting patients with poor outcome early and their early management.

Severe sepsis was present in 33% and septic shock was present in 4% patients. Incidence of septic shock in scrub typhus varies in literature. Vikrant *et al* reported septic shock in 3% of patients however Kumar *et al* reported septic shock in 22% of patients.^{18,19}

Patients with severe sepsis and organ failure were more likely to get ICU admission. Among the criteria used to classify severity of scrub typhus, organ failure was significantly associated with mortality. Possibly it is because that organ failure cut off values used to define organ failure were more stringent and severe sepsis being a less severe manifestation of scrub typhus in same spectrum of disease process. In a study by Varghese *et al*, shock requiring vasoactive agents, CNS dysfunction, and renal dysfunction were independent predictors of mortality.²⁰ Hence presence of organ failure should alert physician towards severe disease. Strict monitoring and ICU care should be provided to such patients to prevent multiple organ failure and mortality.

Limitations

This study had some drawbacks. The data about previous treatment received in peripheral hospitals before admission was not available. This study was conducted in a tertiary care centre, so more severely affected patients requiring intensive management were included in the study, resulting in increased number of patients with severe disease as compared to Primary Health Services.

Conclusion

Scrub typhus can manifest with potentially life-threatening complications such as meningoencephalitis, septic shock, ARDS, acute liver failure, acute kidney injury, severe thrombocytopenia. Leukocytosis, hyperbilirubinemia, transaminitis, hypoalbuminemia, and uremia were associated with organ failure and were significantly associated with mortality.

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