

Coagulation Abnormalities in Severe Scrub Typhus and Their Association with Complications

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ABSTRACT

Aim: To describe coagulation abnormalities and their association with complications in patients with severe scrub typhus.

Materials and methods: A cohort study was conducted among all patients of severe scrub typhus [immunoglobulin M (IgM) positive] who reported to this facility from 1st August 2019 to 31st July 2020 and met our inclusion criteria. We estimated the incidence of severe thrombocytopenia (<50,000/ μ L) and overt disseminated intravascular coagulation (DIC) (DIC score of ≥ 5). We determined the association [risk (RR) ratios] of these abnormalities with complications of scrub typhus, namely—septic shock, multiple organ dysfunction syndrome (MODS), and septic shock with MODS.

Results: In total, 71 patients were studied with a mean age of 50 ± 15.5 years, of which 45 (63.4%) were females. On presentation, fever 70 (98.5%), myalgias 22 (31.0%), loose stools 13 (18.3%), cough, vomiting, headache 11 (15.5%), altered sensorium 10 (14.1%), and pain abdomen 9 (12.7%) were main symptoms. On examination, hypotension 31 (43.7%), eschar 25 (35.2%), icterus 17 (23.9%), and rash 16 (22.5%) were noted.

The d-dimer (>0.5 μ g/mL) levels were increased in all (100%) patients. Thrombocytopenia (91.5%) was the commonest hematological abnormality and 31 (43.6%) of them had severe thrombocytopenia, 25 (35.2%) patients had low fibrinogen levels (<200 mg/dL) and prothrombin time (PT >16.7 seconds) was prolonged in 20 (28.1%).

A total of 42 (59.1%) patients developed MODS, 33 (46.4%) developed septic shock, 24 (33.8%) had MODS with septic shock, 17 (23.9%) developed overt DIC, and eight (11.2%) died. Severe thrombocytopenia ($p = -0.028$) and overt DIC ($p = 0.045$) were significantly associated with septic shock development.

Conclusion: In the patients admitted with severe scrub typhus; thrombocytopenia was the commonest hematological abnormality. The development of septic shock was significantly associated with severe thrombocytopenia and overt DIC.

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INTRODUCTION

Scrub typhus, caused by *Orientia tsutsugamushi*, is an endemic disease in the “tsutsugamushi triangle,” extending from north part of Japan to Northern Australia in the South, the far eastern part of Russia in the North, and to Pakistan in the Western part.¹ The recombinant enzyme-linked immunosorbent assay (ELISA) used for the detection of IgM antibodies for *O. tsutsugamushi* has sensitivity and specificity of 97 and 100%, respectively.²

On the basis of histopathologic studies, scrub typhus causes disseminated vasculitis with perivasculitis. *O. tsutsugamushi* multiplies at the inoculation site leading to necrosis of the skin, forming an eschar with regional lymph node enlargement. *O. tsutsugamushi* infection causes elevation of interferon α , interleukin-18 (IL-18), and IL-15 levels associated with a type 1 immune response.³ The dissemination of *O. tsutsugamushi* infection to vascular endothelium results in vascular injury

affecting multiple organs leading to DIC with platelet consumption, vascular leak, shock, dysfunction of kidneys, liver, pulmonary edema, and meningoencephalitis.⁴

Pathophysiology of DIC in Sepsis

The development of sepsis is commonly associated with hemostatic abnormalities, which can range from insignificant laboratory derangements to severe DIC.⁵ All patients with sepsis have coagulation abnormalities ranging from mild thrombocytopenia, subclinical prolongation of clotting time to fulminant DIC.⁶

The intravascular activation of coagulation without a specific localization characterizes DIC. *O. tsutsugamushi* induces a very strong procoagulant activity leading to an excess of thrombin formation overpowering the mechanisms responsible for maintaining the anticoagulant state maintained due to the effects of protein C, antithrombin, and the tissue factor pathway inhibitor, which results into thrombosis

throughout the vasculature.⁷ It also causes “consumption coagulopathy,” which includes prolonged PTT and PT/international normalized ratio (INR), thrombocytopenia, hypofibrinogenemia, and an increase in D-dimer. DIC can be a hypercoagulable state initially manifesting clinically as thrombosis, embolism, and microvascular occlusion by fibrin thrombi causing tissue ischemia leading to dysfunction of multiple organs (MODS) and simultaneously a hemorrhagic disorder also due to platelets depletion, consumption of various coagulation factors, and/or accelerated plasmin formation manifesting as both thrombosis and bleeding disorders in the same patient.⁸

The availability of literature on the prevalence of coagulation abnormalities in scrub typhus is rather sparse.^{9–11}

MATERIALS AND METHODS

The study was conducted from 1st August 2019 to 31st July 2020 on 71 patients admitted patients with severe scrub typhus

Inclusion Criteria

- Age of >18 years.
- A clinically suspected scrub typhus patient with IgM antibodies positive by ELISA for *O. tsutsugamushi* and fulfilling criteria of severe sepsis or septic shock or MODS.

Exclusion Criteria

The patients were not willing to participate in the study.

Case Definitions

Case—a clinically suspected scrub typhus patient with IgM antibodies positive by ELISA

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for *O. tsutsugamushi* and fulfilling criteria of severe sepsis or septic shock or MODS.

Severe Scrub Typhus

A case of scrub typhus with severe sepsis or septic shock or MODS. The systemic response to proven or suspected infection plus some degree of organ hypofunction that is:

- Cardiovascular: Systolic blood pressure (SBP) of ≤ 90 mmHg or mean arterial pressure (MAP) of < 70 mmHg that responds to the administration of intravenous fluids.
- Renal: Urine output < 0.5 mL/kg/hour for 1 hour despite adequate fluid resuscitation.
- Respiratory: Partial pressure of oxygen/fraction of inspired oxygen of ≤ 250 or, if the lung is the only dysfunctional organ, < 200 .
- Hematological: Platelet count of $< 80,000/\mu\text{L}$ or 50% decrease in platelet count from the highest value recorded over the previous 3 days.
- Unexplained metabolic acidosis: pH of ≤ 7.30 or base deficit of ≥ 5 mEq/L and plasma lactate levels > 1.5 times the upper limit of normal.

Septic Shock

Sepsis with hypotension (SBP of < 90 mm Hg) for at least 1 hour despite fluid resuscitation or need for vasopressors to maintain SBP of > 90 mm Hg or MAP of > 70 mm Hg.¹²

Multiple Organs Dysfunction Syndrome (MODS)

The presence of sepsis causing potentially reversible physiological derangement involving two or more organ systems was defined as MODS.¹³

The patients were included in the present study after obtaining consent. A detailed clinical examination, hematological investigations, including platelet counts and biochemical investigations, were performed. All patients were treated with anti-rickettsial drugs empirically.

The following special hematological investigations were included:

- Prothrombin time (PT): Normal for PT—11.4–13.7 seconds, prolonged PT was defined as prolongation by > 3 seconds.
- International normalized ratio (INR)
- D-dimer: Normal levels— < 0.5 $\mu\text{g/mL}$, > 0.5 – < 4 $\mu\text{g/mL}$ were defined as moderately increased, and levels of > 4 $\mu\text{g/mL}$ were defined as markedly increased.
- Serum fibrinogen: Serum fibrinogen < 200 mg/dL was defined as low fibrinogen. The values of serum fibrinogen were calculated as mg/dL and the

calculation used was serum fibrinogen levels $100/\text{dL} = 1$ gm/L.

- Platelet count: Range—normal range $> 1,50,000/\mu\text{L}$, platelets count $1,50,000/\mu\text{L}$ or less was defined as thrombocytopenia, and platelet counts of $< 50,000/\mu\text{L}$ was defined as severe thrombocytopenia.
- Serum ferritin levels > 2000 ng/mL were defined as raised levels in the study.

The DIC score was calculated as per the diagnostic scoring system for DIC proposed by the International Society for Thrombosis and Hemostasis (ISTH).¹⁴

Diagnostic Scoring System for DIC

Investigation	Value	Score
Platelet count	$> 1,00,000/\mu\text{L}$	0
	$50,000$ – $1,00,000/\mu\text{L}$	1
	$< 50,000/\mu\text{L}$	2
PT prolongation	< 3 seconds	0
	> 3 – < 6 seconds	1
	> 6 seconds	2
Fibrinogen levels	> 1 g/L	> 1 g/L
	< 1 g/L	< 1 g/L
D-dimer	No increase	0
	Moderate increase	2
	Marked increase	3

A calculated DIC score of ≥ 5 was defined as overt DIC.

The data obtained was entered on a Microsoft Excel spreadsheet and Epi Info 7.1.5 for windows was used for data analysis. The patients were classified based

on operational definitions. The p -value of < 0.05 was considered statistically significant. This study was approved by Institutional Ethics Committee.

RESULTS

A total of 71 patients, ranging from 18 to 80 years (mean age was 50 ± 15.5 years), were studied. Forty five (63.4%) were females, 26 (36.6%) were males (male to female ratio 1:1.7). A total of 36 (50.7%) were aged < 50 years and the majority (91.5%) patients were involved in agricultural activities, and 70 (98.5%) cases were observed during monsoon and postmonsoon season.

The details of the main clinical features noted in the study population are given in Table 1. In biochemical investigations, transaminitis in 63 (88.7%), hypoalbuminemia in 62 (87.3%), hyperbilirubinemia in 34 (49.7%), hyponatremia in 30 (42.3%), and raised serum creatinine in 29 (40.8%) patients were observed.

In hematological investigations, severe thrombocytopenia (platelets $< 50,000/\mu\text{L}$) was observed in 30 (42.2%) and 25 (35.2%) had leucocyte abnormalities. Of the total 71 patients, d-dimer (> 0.5 $\mu\text{g/mL}$) levels were raised in all patients, PT (PT of > 16.7 seconds) was prolonged in 20 (28.1%), and low fibrinogen levels (< 200 mg/dL) were noted in 25 (35.2%) patients. The raised serum ferritin levels (> 2000 ng/mL) were observed in 44 (61.9%) patients. The details of special hematological investigations in patients included in the study are given in Table 2.

Of the total 71 patients, only two patients required intensive care unit and 8 (11.2%) died. The details of various complications, that is, septic shock, MODS, septic shock with MODS

Table 1: Clinical features among the study population

Serial no	Clinical feature	Total <i>n</i> = 71 (%)	Female <i>n</i> = 45 (%)	Male <i>n</i> = 26 (%)
1	Fever	70 (98.5)	44 (97.7)	26 (100)
2	Myalgia	22 (31.0)	12 (26.7)	10 (38.5)
3	Loose stools	13 (18.3)	5 (11.1)	8 (30.8)
4	Vomiting	11 (15.5)	6 (13.3)	5 (19.2)
5	Cough	11 (15.5)	7 (15.6)	4 (15.4)
6	Headache	11 (15.5)	8 (17.8)	3 (11.5)
7	Altered sensorium	10 (14.1)	6 (13.3)	4 (15.4)
8	Pain abdomen	9 (12.7)	4 (8.9)	5 (19.2)
9	Seizure	2 (2.8)	1 (2.2)	1 (3.8)
10	Myalgia	22 (31.0)	12 (26.7)	10 (38.5)
11	Loose stools	13 (18.3)	5 (11.1)	8 (30.8)
12	Hypotension	31 (43.6)	15 (33.3)	16 (61.5)
13	Eschar	25 (35.2)	14 (31.1)	11 (42.3)
14	Icterus	17 (23.9)	8 (17.7)	9 (34.6)
15	Rash	16 (22.5)	15 (33.3)	1 (3.8)

and overt DIC, observed in the patients in the study are given in Table 3.

The relationship between various complications observed in the study population with the hematological abnormalities studied in the present study

is given in Table 4. The elevated serum ferritin levels (>2000 ng/mL) were not associated with the complications studied. Thrombocytopenia was the commonest hematological abnormality. There was a significant association between the

development of septic shock with overt DIC ($p = 0.045$) and severe thrombocytopenia ($p = 0.028$).

DISCUSSION

This study was conducted, among admitted patients of scrub typhus, to describe the association of coagulation abnormalities with the development of various complications.

Of the total 71 patients in the study, 45 (63.4%) were females and 26 (36.6%) were males. Sharma et al. and Griffith et al. also reported a higher incidence of scrub typhus in females.^{1,15} The higher incidence in females may be due to the fact that in this region of our country, the females involved in agriculture work with bare hands in a sitting position, and hence their chances of exposure to mites are much higher. The majority of patients in our study were noted in the monsoon and postmonsoon months of September and October, which was similar to a study by Subbalaxmi et al.¹⁶

In this study, fever was present in 98.5% of cases, myalgias were noted in 22 (31.0%), loose stools in 13 (18.3%), headache, cough, and vomiting in 11 (15.5%), altered sensorium in 10 (14.1%). These similar findings of our study are similar to those noted by Tsay and Chang and Mahajan et al.^{2,17} In the present study, eschar was observed in 32 (35.9%), whereas a study by Griffith et al. and Tsay and Chang reported eschar in 41.6 and 60% respectively in patients of scrub typhus.^{15,2}

Of the total 71 patients, thrombocytopenia (<1.5 lakhs/dL) was a major finding observed in 65 (91.5%) patients and 31 (43.6%) of them had severe thrombocytopenia (<50,000/ μ L). The

Table 2: Special hematological investigations among the study population

Serial no	Investigation	Total <i>n</i> = 71 (%)	Female <i>n</i> = 45 (%)	Male <i>n</i> = 26 (%)
1	PT (seconds)			
	>16.7	20 (28.1)	11 (24.4)	9 (34.6)
	>19.7	4 (5.6)	3 (6.6)	1 (3.8)
2	D-dimer (μ g/mL)			
	>0.5	71 (100)	45 (100)	26 (100)
	>1.0–<2	50 (70.4)	40 (88.8)	10 (38.4)
	>2.0–<4	10 (14.0)	5 (11.1)	5 (19.2)
	>4.0	3 (4.2)	2 (4.4)	1 (3.8)
3	Serum fibrinogen (mg/dL)			
	>200	46 (64.7)	29 (64.4)	18 (69.2)
	<200	25 (35.2)	17 (37.7)	8 (30.7)
	<100	8 (11.2)	7 (15.5)	1 (3.8)
4	Platelet (μ L)			
	>1,50,000	6 (8.4)	3 (6.6)	3 (11.5)
	<1,50,000	65 (91.5)	43 (95.5)	22 (84.6)
	50,000–1,00,000	27 (38.0)	19 (42.2)	8 (30.7)
	<50,000	31 (43.6)	18 (40.0)	13 (50.0)
5	Serum ferritin (ng/mL)	<i>n</i> = 70 (%)	<i>n</i> = 45 (%)	<i>n</i> = 25 (%)
	<2000	26 (37.1)	14 (31.1)	12 (48.0)
	>2000	44 (62.8)	31 (68.8)	13 (52.0)

Table 3: The complications observed among the study population

Serial no	Findings	Total <i>n</i> = 71 (%)	Female <i>n</i> = 45 (%)	Male <i>n</i> = 26 (%)
1	MODS	42 (59.1)	28 (62.2)	14 (53.8)
2	Septic shock	33 (46.4)	22 (48.8)	11 (42.3)
3	Septic shock with MODS	24 (33.8)	13 (28.8)	11 (42.3)
4	DIC score \geq 5	17 (23.9)	11 (24.4)	6 (23.0)

Table 4: The association between hematological abnormalities and complications studied (*n* = 71)¹

Association between septic shock and hematological abnormalities among the study population									
Exposure/risk factor	Incidence						RR (%)	95% CI	p-value
	Among exposed		Among unexposed						
	No.	Total	%	No.	Total	%			
Platelet count <50,000	19	30	63.3	14	41	34.1	1.9	1.1–3.1	0.028
DIC score ≥5	12	17	70.6	21	54	38.9	1.8	1.2–2.9	0.045
Serum ferritin >2000 (n = 70)	24	44	54.5	9	26	34.6	1.6	0.9–2.9	0.172
Association between MODS and hematological abnormalities among the study population									
Platelets count <50,000	21	30	70.0	21	41	51.2	1.4	0.9–2.0	0.178
DIC score ≥5	13	17	6.5	29	54	53.7	1.4	1.0–2.0	0.167
Serum ferritin >2000 (n = 70)	28	44	63.6	14	26	53.8	1.2	0.8–1.8	0.579
Association between septic shock with MODS and hematological abnormalities among the study population									
Platelets count <50,000	14	30	46.7	10	41	24.4	1.9	1.0–3.7	0.088
DIC score ≥5	9	17	52.9	15	54	27.8	1.9	1.0–3.5	0.105
Serum ferritin >2000 (n = 70)	19	44	43.2	5	26	19.2	2.2	1.0–5.3	0.075
Association between mortality and hematological abnormalities among the study population									
Platelets count <50,000	3	30	10.0	4	41	9.8	1.0	0.2–4.2	0.712
DIC score ≥5	2	17	11.8	5	54	9.3	1.3	0.3–6.0	0.870
Serum ferritin >2000 (n = 70)	4	44	9.1	3	26	11.5	0.8	0.2–3.2	0.934

occurrence of thrombocytopenia has been reported from 61 to 86% in patients of scrub typhus.^{15,18} A retrospective study reported the presence of lower platelet count than the control population and platelets $<100,000/\text{mm}^3$ were observed more frequently in patients of scrub typhus with bleeding and severe illness.¹¹

In our study, septic shock was present in 33 (46.4%) patients, MODS was observed in 42 (59.1%) patients, and septic shock with MODS was noted in 24 (33.8%). In a study conducted in Meghalaya,¹⁹ MODS were reported in 14.4% of patients. Of the total 71 patients in the present study, 8 (11.2%) patients died; however, Griffith et al. reported mortality in 24.1% of patients with scrub typhus.¹⁵ A study by Thap et al. reported that scrub typhus with septic shock resulted in organ failure and respiratory failure.¹⁸ A retrospective study done in Korea reported MODS in 57.7% of patients.¹¹

In the present study, 60 (84.5%) patients had moderately increased d-dimer and three of them had markedly raised d-dimer levels; 20 (28.1%) patients had prolonged PT, and low fibrinogen levels ($<1 \text{ gm/L}$) were noted in eight (11.2%) patients. The levels of coagulation factors and the presence of DIC in patients with scrub typhus were evaluated in a retrospective study. In total, 365 patients and 36 healthy controls were evaluated for DIC scores. The comparison was done between patients and healthy controls ($p < 0.001$ for all tests) by comparing median concentrations of fibrinogen, d-dimer, and fibrin/fibrinogen degradation products. PT was prolonged in patients of scrub typhus than the controls. When compared, the patients of severe scrub typhus were associated more significantly with PT prolongation, increased d-dimer levels along with fibrinogen degradation products and decreased fibrinogen levels in comparison to less severe scrub typhus.¹¹

In our study, overt DIC was observed in 17 (23.9%) patients. A study by Thap et al. documented the occurrence of DIC in patients with scrub typhus.²⁰ In a retrospective study, the DIC scores (ISTH criteria) were calculated in 365 patients of scrub typhus, 51 patients fulfilled the criteria of severe scrub typhus, and the remaining 314 were in nonsevere group. Overt DIC was observed in 13.7% of patients with severe scrub typhus, whereas only 2.7% of patients in nonsevere group had overt DIC; it concluded that coagulation system activation was an important feature of scrub typhus and it also correlated with the severity of scrub typhus.¹¹

Voves et al. calculated the DIC score (ISTH criteria) in patients with severe sepsis (32 patients) and those with septic shock (eight patients). The DIC scores calculated for nonsurvivors group and those in the septic shock group were significantly higher in comparison to the survivor's group and severe sepsis group. The presence of overt DIC had a significantly higher risk of death and septic shock. The prolongations of the PT and platelet counts were strongly linked to the DIC score. They concluded that the DIC score was very useful in identifying patients with activation of coagulation cascade hence predicting disease severity and fatality.²¹

In the present study, septic shock ($p = 0.028$, RR 1.9, and 95 % confidence of interval (CI) 1.1–3.1) was significantly associated with severe thrombocytopenia. The associations of severe thrombocytopenia with other complications studied, MODS ($p = 0.178$) and septic shock with MODS ($p = 0.088$), were not significant; however, higher risk ratios of 1.4 and 1.9 were observed with these complications, respectively.

The presence of overt DIC was also significantly associated with the development of septic shock ($p = 0.045$, RR 1.9, and 95% CI 1.2–2.9), but overt DIC was not significantly associated, but higher risk ratios were observed with the development of MODS (1.4), septic shock with MODS (1.9) and death (1.3).

The study was underpowered to detect associations between severe thrombocytopenia and overt DIC with the development of MODS and septic shock with MODS due to the smaller sample size of the study population.

CONCLUSION

In patients admitted with severe scrub typhus, thrombocytopenia was the commonest hematological abnormality noted, and the presence of severe thrombocytopenia and overt DIC were associated with the development of septic shock.

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