

Clinical Score to Differentiate Scrub Typhus and Dengue: A Tool to Differentiate Scrub Typhus and Dengue

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Abstract

Background: Dengue and scrub typhus share similar clinical and epidemiological features, and are difficult to differentiate at initial presentation. Many places are endemic to both these infections where they comprise the majority of acute undifferentiated febrile illnesses. **Materials and Methods:** We aimed to develop a score that can differentiate scrub typhus from dengue. In this cross-sectional study, 188 cases of scrub typhus and 201 cases of dengue infection who presented to the emergency department or medicine outpatient clinic from September 2012 to April 2013 were included. Univariate followed by multivariate logistic regression analysis was performed to identify clinical features and laboratory results that were significantly different between the two groups. Each variable was assigned scores based on the strength of association and receiver operating characteristics area under the curve (ROC-AUC) was generated and compared. Six scoring models were explored to ascertain the model with the best fit. **Results:** Model 2 was developed using the following six variables: oxygen saturation (>90%, ≤90%), total white blood cell count (<4000, 4001–7000 and >7000 cells/cumm), hemoglobin (≤14 and >14 g/dL), total bilirubin (<2 and ≥2 mg/dL), serum glutamic oxaloacetic transaminase (>200 and ≥200 IU/dL), and altered sensorium (present or absent). Each variable was assigned scores based on its strength of association. The AUC-ROC curve (95% confidence interval) for model 2 was 0.84 (0.79–0.89). At the cut off score of 13, the sensitivity and specificity were 85% and 77% respectively, with a higher score favoring dengue. **Conclusion:** In areas of high burden of ST and dengue, model 2 (the “clinical score to differentiate scrub typhus and dengue fever”) is a simple and rapid clinical scoring system that may be used to differentiate scrub typhus and dengue at initial presentation.

Keywords: Clinical score to differentiate scrub typhus and dengue score, dengue fever, scoring system, scrub typhus

INTRODUCTION

Scrub typhus and dengue are two major causes of acute undifferentiated febrile illness and are endemic in many parts of India and the Asia Pacific region.^[1-5] In many parts of India, these two infections together comprise more than half of all acute undifferentiated febrile illnesses.^[3] Both the infections share similar clinico-epidemiological features and are difficult to differentiate at initial presentation. The causative agent of scrub typhus is a Gram-negative intracellular bacterium, *Orientia tsutsugamushi*, which is inoculated into humans by the bite of an infected larva of trombiculid mites (*Leptotrombidium* species). The pathogenesis is immune mediated lymphohistiocytic vasculitis and frequently results in multiple organ dysfunction.^[6,7] Delay in diagnosis and initiation of appropriate antibiotic therapy can be associated with mortality in 14%–20% of patients.^[2,6-8] Hence, early recognition and prompt antibiotic therapy is crucial in the

management of ST. Dengue is a mosquito-borne infection caused by one of the four dengue virus serotypes that belong to the genus *Flavivirus*. Despite supportive management, mortality rate due to dengue hemorrhagic fever and dengue shock syndrome (DSS) ranges from 3% to 11% among adults.^[9,10] Early diagnosis can improve patient outcomes and promote timely public health interventions. Both these infections peak during the monsoon season in many parts of India. A pathognomonic eschar, which is probably the most important diagnostic clue for scrub typhus can be

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identified in only 20%–54% of patients.^[3,8,11,12] In its absence, scrub typhus and dengue are virtually indistinguishable at presentation. Diagnostic tests for scrub typhus (enzyme-linked immunosorbent assay [ELISA] for immunoglobulin M [IgM]) and dengue (reverse transcriptase-polymerase chain reaction [RT-PCR] or IgM ELISA) have many limitations.^[13] They are time-consuming, labor intensive, expensive and not available at the point of care in most centers in developing countries. In this prospective study, we aimed to investigate the differences in clinical features and easily available laboratory parameters between scrub typhus and dengue febrile illness and develop a scoring model, “clinical score to differentiate scrub typhus and dengue (CSSD),” which can aid in differentiating scrub typhus from dengue at presentation.

MATERIALS AND METHODS

Study design and setting

This cross-sectional observational study was conducted at Christian Medical College, Vellore, which is 2700 bedded tertiary care teaching hospital in South India. Adult patients (age ≥ 16 years) presenting to the emergency department (ED) or medical outpatient clinic between September 2012 and April 2013 with acute febrile illness (temperature $\geq 101^\circ\text{F}$ of 3–14 days duration) and diagnosed to have scrub typhus or dengue were enrolled.

A detailed history and results of a thorough physical examination were entered on a standard data collection sheet after obtaining a written informed consent. The routine baseline investigations included complete blood count analysis, serum electrolytes, liver and renal function tests. Pulse oximeter saturation (SpO_2) was measured for all patients at presentation and recorded. A thin smear was performed to detect malarial parasites. A single blood culture was obtained from all enrolled patients in an aerobic BacT/Alert 3D (BioMerieux, Hazelwood, MO, USA) bottle and incubated for up to 7 days in the BacT/Alert blood culture system. All commercial ELISA tests were performed for agents believed to be endemic to the region and interpreted according to the manufacturer’s instruction as positive, equivocal, and negative. These serological tests were done on or after the 7th day of fever and included dengue IgM ELISA (Dengue Duo Cassette, PanBio), scrub typhus IgM ELISA (In Bios International Inc., Seattle, WA, USA), leptospira IgM ELISA (Virion/Serion GmbH, Germany) and a Widal test. By protocol, all patients with fever < 7 days were followed up and serological tests were sent only on or after the 7th day of fever. Influenza PCR testing was done in all patients with upper respiratory symptoms such as a cough, rhinorrhea, and breathlessness. It was not routinely tested if patients had a pathognomonic eschar or had classical presentation of dengue without upper respiratory symptoms. Altered sensorium was defined as a Glasgow coma scale < 15 .

Diagnostic criteria for scrub typhus and dengue fever:

- Scrub typhus: Eschar + Scrub IgM ELISA positive or Scrub IgM ELISA positive with other common causes of

acute undifferentiated fever (malaria, enteric fever, other bacteremia, dengue, leptospirosis) ruled out

Dengue fever:

- Clinical features of dengue as per the syndromic case definition suggested by the World Health Organization (WHO, 2009)^[14] PLUS
- Laboratory confirmation by Dengue IgM ELISA positive PLUS
- Other common causes of acute undifferentiated fever (malaria, enteric fever, other bacteremia, scrub typhus, leptospirosis) ruled out.

Statistical methods

The data were entered into a Microsoft Excel sheet (version 2007). Statistical analysis was performed using Statistical Package for Social Sciences for Windows (SPSS Inc. Released 2007, version 16.0. Chicago, IL, USA). Mean (SD) or median (range) were calculated for the continuous variables and *t*-test or Mann–Whitney test was used to test the significance. The categorical variables were expressed in proportion and Chi-square test or Fisher exact test was used to compare dichotomous variables. Univariate analysis was performed to identify the baseline clinical and laboratory variables that were significantly different between the two groups. These variables were incorporated for multivariate logistic regression analysis to examine the relationship between the binary and continuous variables that could identify those that significantly differentiate the two groups. For all tests, a two-sided $P \leq 0.05$ was considered statistically significant. Different models were developed using scores based on the strength of association (odds ratio [OR]) and assigning simpler scores based the relative weightage of the OR. Receiver operating characteristics area under the curve (ROC-AUC) was generated and compared to identify the best fit model. Since our aim was to create a simple scoring system that can be used to differentiate dengue and scrub typhus using basic clinical and laboratory features, we included only those variables that are relevant and readily available in a few hours in most hospitals.

This study was approved by the Institutional Review Board (Min. No. 8007 dated 19/09/2012) and patient confidentiality was maintained using unique identifiers and by password protected data entry software with restricted users.

RESULTS

During the study, a total of 1068 patients presented with acute undifferentiated febrile illness. 188 patients with scrub typhus and 201 patients with dengue fever were enrolled prospectively in the study. The mean age of the patients was 41.6 ± 14.8 years in the scrub typhus group and 29.8 ± 12.5 years in the dengue group (95% confidence interval [CI] = 8.9–14.4, $P < 0.001$). There was a female predominance (56.4%) in the dengue group and a male predominance (55.7%) in the scrub typhus group ($P = 0.03$). The mean duration of fever before

the presentation was significantly longer in the scrub typhus group (8.1 ± 3 days) as compared to the dengue group (5.9 ± 2.5 days; 95% CI 1.6–2.7). A pathognomonic eschar was found in 53.7% of patients with scrub typhus. The mean white blood cell (WBC) count, platelet count and total bilirubin were higher in scrub typhus group than dengue group, whereas the mean hemoglobin and serum glutamic oxaloacetic transaminase (SGOT) level was significantly higher in the dengue than scrub typhus group. Common symptoms in both the groups included breathlessness, dry cough, nausea, vomiting, headache, myalgia, altered sensorium, abdominal pain, and bleeding. Patients in the scrub typhus group had higher prevalence of a cough, breathlessness, and altered sensorium. The baseline clinical characteristics and the laboratory investigations are shown in Table 1.

Based on the multivariate logistic regression analysis, seven variables with the highest OR and $P < 0.05$ were selected. The seven variables were categorized, based on arbitrary cut off values, into two or three groups as follows: oxygen saturation ($>90\%$, $\leq 90\%$), age (>30 and ≤ 30 years), total WBC count (<4000 , $4001-7000$ and >7000 cells/cumm), hemoglobin (≤ 14 and >14 g/dL), total

bilirubin (≤ 2 and >2 mg/dL), SGOT (>200 and ≤ 200 IU/dL), and altered sensorium (present or absent). Each variable was assigned a score based on the OR obtained from the regression model (stronger the association higher the score) [Table 2].

Derivation of the prediction models

Six out of seven variables (excluding age) were used to derive four scoring models (model 1, 2, 3, and 4). [Table 3] Model 1 was developed based on scores assigned as per the observed OR in the multivariate analysis. To simplify the scores of model 1, we derived model 2 and model 3 based on the relative weightage of the OR. Similarly, in model 4 we assigned scores of 0 or 1 for each of the six variables where 1 represents the odds of the actual disease state (dengue) as compared to scrub typhus followed by the next variable. The difference between model 3 and model 4 was that $SpO_2 < 90\%$ was assigned a score of 3 in model 3 and a score of 0 in model 4. In model 5 and 6, only 2 variables (age and total WBC counts) were used. Model 5 was developed based on scores assigned based on observed OR while model 6 was developed based on simplified scores. ROC curve was generated to compare the six scoring models [Figure 1]. The AUC-ROC (95% CI) for models 1–6 were 0.83 (0.78–0.88); 0.84 (0.79–0.89); 0.79 (0.73–0.82); 0.80 (0.75–0.86); 0.77 (0.71–0.83); and 0.80 (0.75–0.86), respectively. Among these, model 2 was found to be the simplest and had the best diagnostic accuracy to differentiate dengue from scrub typhus. At the cut off score of 13, the sensitivity and specificity to diagnose dengue was 85% and 77%, respectively. One clinical feature (altered sensorium) and five simple laboratory tests that are readily available at most health facilities were the variables used in this model [Table 4].

Leukopenia is a feature of dengue, while leukocytosis is found in scrub typhus. Model 6, which is based only on age and WBC counts, has an AUC of 0.8 (95% CI = 0.75–0.86), which is comparable to model 2. Hence, if liver function tests are not available, age and WBC count may be used to differentiate between scrub typhus and dengue.

Table 1: Baseline Clinical Features and Laboratory Investigations

Variables	Scrub typhus (n=188)	Dengue (n=201)	P
Age (years)*	41.6±14.8	29.8±12.5	<0.001
Male, n (%)	82 (43.6)	111 (55.2)	0.03
Female, n (%)	106 (56.4)	90 (44.8)	
Duration of fever (days)*	8.1±3.0	5.9±2.6	<0.001
Myalgia, n (%)	152 (80.9)	174 (86.6)	0.13
Arthralgia, n (%)	10 (5.3)	14 (7.0)	0.53
Headache, n (%)	126 (67)	128 (63.9)	0.52
Seizure, n (%)	7 (3.7)	3 (1.5)	0.2
Altered sensorium, n (%)	11 (5.2)	2 (1.0)	0.009
Vomiting, n (%)	88 (46.8)	99 (49.3)	0.58
Abdominal pain, n (%)	44 (23.4)	39 (19.4)	0.38
Breathlessness, n (%)	58 (30.9)	8 (4.0)	<0.001
Cough, n (%)	35 (18.6)	23 (11.4)	0.06
Overt bleeding, n (%)	10 (5.3)	19 (9.5)	0.12
Lymphadenopathy (%)	8 (4.2)	2 (0.9)	<0.001
Rash (%)	9 (4.8)	35 (17.4)	<0.001
SpO ₂ (%)*	94±5.7	97±2.2	<0.001
SpO ₂ <90 (%)	19 (10.1)	3 (1.4)	<0.001
Hemoglobin (g), %*	12.7±2.0	14.6±2.0	<0.001
Total WBC count (cells/μL)*	9836±6447.0	5227±4132	<0.001
Platelet count (cells/μL)*	112,000±84,899	81,500±65,500	<0.001
Total bilirubin (mg/dL)*	1.4±1.9	0.7±0.45	<0.001
SGOT (U/L)*	122±153.7	162.5±202.8	<0.03

*Mean±SD. WBC: White blood cell, SGOT: Serum glutamic oxaloacetic transaminase, SD: Standard deviation

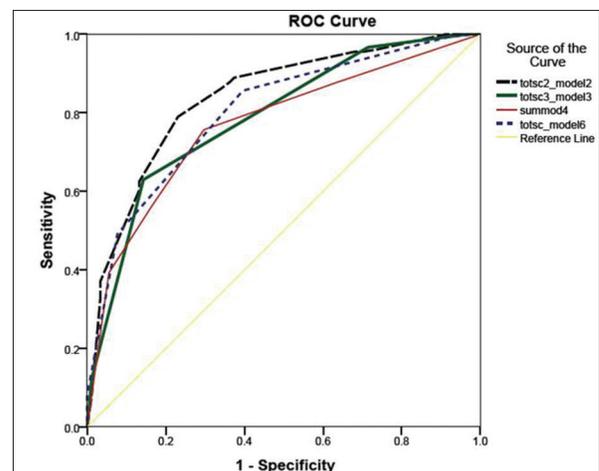


Figure 1: Receiver operating characteristics curve comparing the various scoring models

Table 2: Multivariate Logistic Regression Analysis for Significant Parameters Between Scrub Typhus and Dengue

Variable	Multivariate analysis			
	Scrub typhus, <i>n</i> =188 (%)	Dengue, <i>n</i> =201 (%)	Adjusted OR*	95% CI#
Age (years)				
>30	140 (74)	77 (38.3)	3.82	2.32-6.29
<30	48 (26)	124 (61.6)		
SpO ₂				
>90	171 (91)	198 (98.5)	6.60	1.41-30.85
<90	17 (9)	3 (1.5)		
Hb (g/dL)				
≤14	143 (76)	69 (34.3)	7.91	4.54-13.78
>14	45 (24)	132 (65.7)		
Total WBC count (cells/cumm)				
<4000	15 (8)	102 (51)		
4001-7000	43 (23)	57 (28.5)	17.84	9.16-34.75
>7000	129 (69)	41 (20.5)	3.91	2.24-6.82
Serum bilirubin (mg)				
>2	29 (15.5)	4 (1.9)	5.57	1.64-18.89
<2	159 (84.5)	197 (98.1)		
SGOT (IU/dL)				
>200	22 (11.7)	50 (24.8)	3.05	1.33-6.97
<200	166 (88.3)	151 (75.2)		
Altered sensorium	11 (5.8)	2 (0.9)	3.01	0.55-16.24
No altered sensorium	177 (94.2)	199 (99.1)		

*OR: Odds ratio, #CI: Confidence interval. WBC: White blood cell, SGOT: Serum glutamic oxaloacetic transaminase

DISCUSSION

Scrub typhus and dengue remain the main vector-borne diseases causing acute undifferentiated febrile illness in the “tsutsugamushi triangle.” Despite the difference in pathogenesis, both share the same seasonal distribution, demographic and clinical features and if not recognized early, they are associated with significant mortality.^[3] Early recognition of scrub typhus is important for prompt initiation of appropriate antibiotics. On the other hand, there is currently no antiviral therapy for dengue fever and treatment is largely supportive, with emphasis on adequate hydration. Patients with DSS need aggressive fluid replacement and close monitoring of hemorrhagic complications. In most areas endemic to dengue, there is a deep public stigma associated with it. Patients often consider dengue as the most likely cause of their fever as scrub typhus is not a well-known entity among the public. Early ruling out of dengue at first visit with just the basic investigations while awaiting the results of confirmatory tests may help relieve patient anxiety. Hence, we propose this scoring system that is simple, inexpensive, rapid and is not technically demanding to differentiate between ST and dengue within few hours of presentation to the health care set-up.

Our study findings will certainly be useful for clinicians working in areas where dengue and scrub typhus are common. In Vellore and many parts of India, scrub typhus, and dengue infection are the two most frequently listed presumptive diagnoses in patients who present with fever of undifferentiated

pattern.^[3] Predictors of severity of scrub typhus and dengue and scoring systems to identify severe illness have been described by many researchers in the past.^[15-18] A systematic review identified 15 studies that have examined the differences in clinical and laboratory features between dengue and other febrile illnesses.^[19] Chrispal *et al.* reported leukocytosis, elevated serum alanine aminotransferase, low serum albumin, acute respiratory distress syndrome and the presence of aseptic meningitis to be significant predictors of scrub typhus when compared to other acute undifferentiated febrile illness.^[3] In the same study, WBC count <11,500 cells/mm³, platelet count <50,000 cells/mm³, elevated SGOT and bleeding manifestations were found to be significant predictors of dengue fever.^[3] A few studies to identify distinguishing characteristics between the two infections have also been done. Watt *et al.* reported hemorrhagic manifestations, low platelet count (<140,000/mm³) and low WBC count (<5000/mm³) to be significantly associated with dengue when compared to scrub typhus.^[20] Pulmonary involvement, commonly interstitial pneumonitis, and acute respiratory distress syndrome may be seen in up to 25%–55% of patients with scrub typhus and much less so in dengue fever. Hence, SpO₂ was used as a parameter in differentiating these two infections.^[3] Although these studies clearly identified the differentiating features of scrub typhus and dengue, no attempt was made to develop an easy scoring system that may be used in resource-limited settings. To the best of our knowledge, our proposed scoring system is the first of its kind.

Table 3: Score Assignment Scheme for Classifying Dengue and Scrub Typhus Infection

Variables	Assigned score					
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Age (years)						
≤30	-	-	-	-	4	1
>30	-	-	-	-	0	0
SpO ₂ (%)						
>90	5	4	1	1	-	-
≤90	0	1	3	0	-	-
Total WBC count (cells/μL)						
≤4000	19	7	1	1	18	2
4001-7000	4	3	1	1	4	1
>7000	0	1	0	0	0	0
Hemoglobin (g), %						
>14	8	6	1	1	-	-
≤14	0	1	0	0	-	-
Total bilirubin (mg), %						
>2	0	1	1	1	-	-
≤2	6	5	0	0	-	-
SGOT (IU/L)						
>200	8	2	1	1	-	-
≤200	0	1	0	0	-	-
Altered sensorium						
Present	0	0	0	0	-	-
Absent	2	1	1	1	-	-
Total score						
Minimum	0	0	1	0	3	0
Maximum	42	25	8	6	41	3
AUC	0.83	0.84	0.79	0.8	0.77	0.8
95% CI	0.78-0.88	0.79-0.89	0.73-0.84	0.75-0.86	0.71-0.83	0.75-0.86

AUC: Area under curve, CI: Confidence interval, WBC: White blood cell, SGOT: Serum glutamic oxaloacetic transaminase

Table 4: Clinical Score to Differentiate Scrub Typhus and Dengue Score (Model 2)

Variables	Value	Score
SpO ₂ (%)	>90	4
	<90	1
Hemoglobin (g), %	>14	6
	<14	1
Total WBC count (cells/cumm)	<4000	7
	4000-7000	3
	>7000	1
SGOT (U/L)	>200	2
	<200	1
Serum bilirubin (mg), %	>2	1
	<2	5
Altered sensorium	Yes	0
	No	1
Total score	Range=5-25	
Interpretation		
Total score		
<13	Favors scrub typhus	
>13	Favors dengue	

SGOT: Serum glutamic oxaloacetic transaminase, CI: Confidence Interval, WBC: White blood cell

In the multivariate analysis, seven clinical variables (age, SpO₂, altered sensorium, hemoglobin, total WBC count, total bilirubin, and SGOT level) were found to be significantly different between the ST and dengue groups. These findings were consistent from earlier studies on ST and dengue from Southeast Asia region.^[3,6] Hence, we included these seven variables in the scoring model. The model 1 was derived based on direct OR to the six variables. This yielded a sensitivity of 83% (78%–88%). Since the scores assigned to the variables were cumbersome, we derived and tested models 2, 3 and 4 by assigning simpler scores to the same six variables. The sensitivity of these models was 84% (79%–89%), 79% (73%–84%), and 80% (75%–86%), respectively. Thus, among these three models, model 2 performed the best. Using dichotomous age ranking scores, model 5 and 6 were assessed. However, there was no improvement seen in the performance of these scoring models when compared to model 2. Overall, the sensitivity and false positive rate of the model 2 was the best. Hence, we propose that in endemic areas model 2 may be used as a simple CSSD in acute care settings for early institution of appropriate therapy.

Our study has several strengths. In contrast to many previous studies, data were collected prospectively and recorded at

the time of the initial clinic or ED visit and not at the time of hospitalization. The diagnostic criteria we used, incorporated both clinical features and laboratory confirmation, thereby reducing the potential for misclassification bias. Finally, our study had a relatively large sample size compared with other similar studies.

Nonetheless, the study has several limitations. RT-PCR, which is the recommended confirmatory test for dengue was not used routinely because of financial constraints. The data are from only one region of India and may not be representative of other areas with different scrub typhus serotypes, transmission patterns, population demographics, underlying etiology of acute undifferentiated febrile illness. Further prospective studies are required to validate our scoring system in other geographic settings and time periods.

CONCLUSION

In areas of high burden of ST and dengue, model 2 (the “CSSD”) is a simple and rapid clinical scoring system that may be used to differentiate ST and dengue at initial presentation.

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Conflicts of interest

There are no conflicts of interest.

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