Original Article

A Clinical and Laboratory Scoring Model for Early Differentiation of Dengue and Scrub Typhus Infection

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Abstract

Background : Dengue fever and Scrub Typhus are the most common causes of acute febrile illness in tropical and subtropical areas of the World. The clinical and laboratory features of both infections are often similar, making differentiation challenging during the initial presentation. The aim of this study was to observe the differences in clinical and laboratory characteristics between these two infections and to design a clinical scoring model that may be used as a guide for early detection of these infections.

Materials and Methods : We conducted a cross-sectional study among 184 patients confirmed to have either Dengue or Scrub Typhus. Various clinical and laboratory variables were studied. A scoring model based on nine variables-age, altered sensorium, hemoglobin, total leucocyte count, neutrophil-lymphocyte ratio, platelet count, total bilirubin, CRP, albumin was formed. A cut-off score of four was calculated using a ROC curve.

Results : When validated, this scoring model showed sensitivity of 72% for Dengue and 48% for Scrub Typhus.

Conclusion : Dengue and scrub typhus can have appreciable clinical and laboratory overlap. The scoring model can be used for earlier diagnosis and expedite management.

Key words : Dengue, Scrub Typhus, Scoring Model, Acute Febrile Illness.

Dengue and Scrub Typhus account for more than half of all acute febrile illnesses in several parts of India, including Karnataka and peak during the rainy season[1]. Dengue fever is spread by Aedes mosquitoes. It is caused by one of the four Dengue virus serotypes (DEN-1, DEN-2, DEN-3 and DEN-4) of the Flavivirus genus. Dengue fever presents with a wide range of clinical manifestations with an unpredictably variable clinical course and outcome. Despite supportive therapy, published research in India reported a death rate of 3% to 11% among adults owing to DHF and DSS[2]. Patient outcomes can be improved with early diagnosis and supportive treatment, as well as cautious hydration management and constant monitoring[3].

Scrub Typhus infection is caused by infection with the intracellular bacterium, Orientia tsutsugamushi, which is transmitted to humans by the bite of an infected larva of trombiculid mites[4]. According to reports, eschar, a diagnostic hint for Scrub Typhus infection, is not always present and is only seen in 20-87% of scrub typhus patients[5]. Scrub Typhus responds quickly to antibiotic treatment, with patients becoming afebrile in 24 to 48 hours. The mortality rate in severe cases of multi-organ failure might be as high as 24%[6,7]. Dengue fever (NS1-antigen or IgM Dengue ELISA) and Scrub Typhus (IgM ELISA) diagnostic tests are time-consuming and can result in false positives due to prior infections or cross-reactivity in serological assays[8].

Editor's Comment :

- There is an overlap of clinical features and laboratory investigations between Dengue and Scrub Typhus.
- A scoring model based on nine variables which gave a cut off score of 4. A score of <4 suggested Dengue and >4 suggested Scrub Typhus. When validated, this score demonstrated a sensitivity of 72% for Dengue and 48% for Scrub Typhus.
- Believe that this scoring model when used for a larger population can provide early clue to disease etiology which can guide better treatment decision making and improve patient outcome.

The aims and objectives of this study are to study the clinical and laboratory features to differentiate Dengue and Scrub Typhus infections at presentation and to develop a clinical scoring model to identify the differences in the characteristics of these infections during their initial stages.

Materials and Methods

A cross-sectional observational study was conducted at Kasturba Hospital, Manipal between September, 2019 and September, 2021. Sample size of 164 was calculated

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using the formula:

$Z_{1-\alpha/2}(AUC)/d^2$, where $Z_{1-\alpha/2}$ is the standard normal variate (1.96 at $p<0.05$), AUC is derived from previous studies and d^2 represents the absolute error.

Adults ≥18 years of age admitted to Medicine wards with the diagnosis of Dengue or Scrub Typhus infection confirmed by serological tests were recruited in our study. Patients with evidence of a primary focus of infection (eg, consolidation on chest x-ray, symptoms and signs of urinary tract infection, cellulitis), patients with concurrent culture proven bacterial infections and patients with concomitant febrile illnesses along with Dengue or Scrub Typhus infection such as malaria, leptospirosis, typhoid and influenza were excluded from the study. Since this study was done during the COVID pandemic, patients who were tested COVID positive were excluded from our study.

Demographic data including age, sex, occupation, area of residence, and clinical data including symptoms, vital signs and examination findings were individually collected on study case record forms after obtaining written informed consent. Routine laboratory parameters, such as complete blood count, liver and renal function tests, serum electrolytes, and blood sugars were noted. Chest x-ray findings were noted if done. Oxygen saturation (SpO_2) by pulse oximeter was checked if the patient was breathless or tachypnoeic. Confirmation of dengue positivity was done by assessing dengue-specific IgM antibodies using the kit from National Institute of Virology, Pune. The presence of Dengue non-structural glycoprotein-1 (NS1) antigen was tested using the Pan bio-ELISA kit. Presence of Scrub Typhus infection was confirmed by Scrub Typhus IgM ELISA (In Bio-USA). The illness outcome was assessed in terms of course in the hospital and duration of hospital stay. The patient condition at the time of discharge was noted (survivors/non-survivors).

Study Definitions :

Dengue fever was diagnosed based on compatible clinical and laboratory features as per WHO 2009 classification, with a positive test for non-structural protein (NS1) antigen or Dengue IgM antibodies by ELISA (Pan Bio ELISA). Scrub Typhus was diagnosed based on the presence or absence of eschar, with a positive test for Scrub IgM antibodies by ELISA (In Bio-USA). The Institutional Ethics Committee provided approval for the study (IEC No.: 621/2019) before commencement of data collection.

Statistical Methods :

Sample size was calculated based on classification ability of the scoring system for distinguishing between Dengue and Scrub Typhus. Previous studies have demonstrated an area under the ROC curve of 0.8 based on 6 studies. Anticipating an increase of 7.5% in the area under the ROC curve by incorporating potential clinical and laboratory variables, the minimum required sample size in each group was 82 (total 164). An additional 25 samples for each group were taken for the validation of the derived score. The P value was calculated using Fisher's test for the comparison of clinical and laboratory parameters between the two groups. Based on these findings, a scoring model was developed with arbitrary cut off values. ROC curve demonstrated that for a cut off score of 4, the sensitivity would be 84.1%.

SPSS for Windows version 10.0 was used to gather and analyze the data. The average Standard Deviation was used to represent quantitative data. The Mann–Whitney U-test was used to establish statistical significance for continuous variables, while Fisher's exact test/Chi-square test was used for dichotomous variables. Statistical significance was defined as a P-value of <0.05.

Results

A total of 164 patients were enrolled, comprising 82 patients with dengue and 82 patients with Scrub Typhus. The mean age of Dengue patients was 33.9 years, while that of Scrub Typhus patients was 46.4 years. In the Dengue group, the majority of patients were within the age group of 21-30 years (n=32, 39.02%). In Scrub Typhus, most patients were in the age group of 41-50 years (n=21, 25.60%). Males outnumbered females in both groups, with 67 males (81.7%) and 15 females (18.3%) in the Dengue group, and 46 males (56.3%) and 36 females (43.9%) in the Scrub Typhus group. The maximum number of dengue cases were from Udupi district (n=33, 40.2%), followed by Uttara Kannada (n=13, 15.8%). In contrast, the maximum number of Scrub Typhus cases were from Davangere district (n=23, 28.04%), followed by Chitradurga (n=14, 17.07%).

On the analysis of symptoms in both infections, fever was most common, with 80 cases (97.56%) in Dengue and 77 cases (93.9%) in Scrub Typhus, followed by Myalgia with 51 cases (62.6%) in dengue and 37 cases (45.1%) in Scrub Typhus. The mean duration of fever was 4.79 days in Dengue and 7.25 days in Scrub Typhus. Skin rash was present in 26.8% of Dengue patients (n=22) and 4.8% of scrub typhus patients (n=4). Eschar was present in 17.07% of Scrub Typhus patients and lymphadenopathy was present in 2.4% of Scrub Typhus patients. Altered sensorium was noted in 7.3% of Scrub typhus patients (n=6). Jaundice was reported in 40.2% of Scrub Typhus patients, while only 4.8% of Dengue patients had Jaundice. The mean duration of hospital stay was 4.15 days for Dengue and 6.00 days for Scrub Typhus.

The mean pulse was 84.43 ± 12.31 per minute in Dengue and 93.46 ± 18.78 in Scrub Typhus. Mean SBP (mmHg) and DBP (mmHg) was 112.01 ± 19.85 and 72.44 ± 8.10 in Dengue respectively and 111.95 ± 13.74 and 71.16 ±

11.82 in Scrub Typhus respectively. The mean temperature recorded was 98.58 ± 0.36 in dengue and 98.9 ± 0.98 in Scrub Typhus. More number of patients with Scrub Typhus had hepatomegaly (18.2%) when compared to Dengue (7.3%), whereas Splenomegaly was more common in Dengue (9.7%) than Scrub Typhus (6%).

Complications such as hepatitis, acute kidney injury, encephalitis, ARDS, myocarditis and pancreatitis were more frequently observed in the Scrub Typhus group compared to Dengue. Polyserositis was more common in Dengue, as shown in the graph below. Mortality was seen in the Scrub Typhus group (n=1, 3.5%). The cause of mortality in the Scrub Typhus group was multi-organ dysfunction syndrome. Laboratory investigations done has been summarized in Table 1.

Variables with significant values were selected to devise a scoring model. The nine variables were divided into two groups based on arbitrary cut-off values. A cut-off score was then calculated using a ROC curve to distinguish between the two illnesses.

The model (Fig 1) has a classification ability of 80% (Area under ROC curve), with cut off value of 4.5 with 84.1 % sensitivity and 55% specificity. Therefore, a cut off score of 4 was chosen. A total score of <4 suggested Dengue, and >4 suggested Scrub Typhus.

This model was applied to another subset of patients, with 25 patients in each group for both Dengue and Scrub Typhus, and the results were obtained as mentioned in Table 2. The sensitivity was 72% and 48% when applied on patients who were tested positive for Dengue and Scrub Typhus respectively.

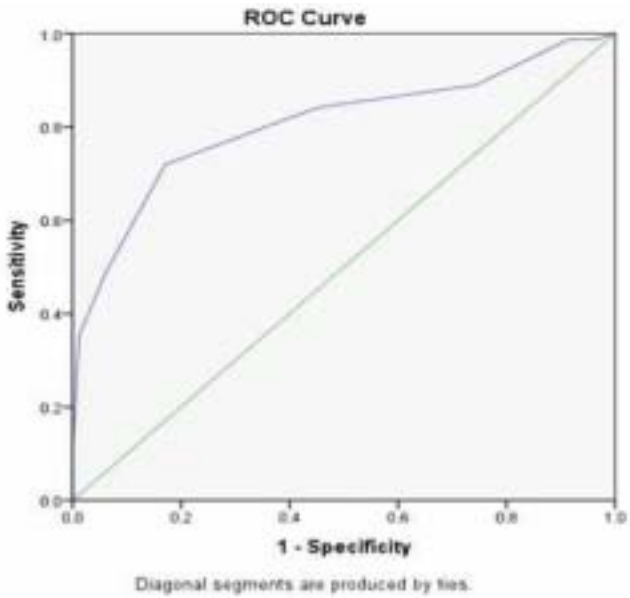

Fig 1 — ROC curve of age, hemoglobin, TLC, NLR, platelets, total bilirubin, CRP, albumin and altered sensorium

Males outnumbered females in the current study, which is in contrast to study in Vellore by Mitra, *et al* where there was male preponderance in Scrub group (55.7%) and female in Dengue (56.4%)[9]. In both Dengue and Scrub Typhus, the mean age was 33.9 years and 46.4 years, respectively, which was similar to the earlier research in Vellore, where the mean age was 29.8 years in Dengue. The possible explanation for male preponderance in all studies could be due to increased outdoor activity, leading to increased exposure to mosquito bites.

Discussion

There is an overlap of clinical features and laboratory investigations between Dengue and Scrub Typhus. Early detection is important to prevent significant morbidity and mortality. The mainstay of treatment for Dengue is supportive management and for Scrub Typhus, it is antibiotics.

Table 2 — *Scoring model for differentiation of Dengue and Scrub Typhus*

Variables	Score 0	Score 1
Age (years)	<40	>40
Haemoglobin (gm/dL)	<14	>14
TLC (cells/µL)	<4000	>4000
NLR	>2	<2
Platelets (cells/µL)	<50000	>50000
Total bilirubin (mg/dL)	<1.2	>1.2
CRP (mg/L)	<6	>6
Albumin (gm/dL)	>3.5	<3.5
Altered sensorium	Absent	Present

Table 1 — *Laboratory features in Dengue and Scrub Typhus*

Laboratory Features	Dengue (n=82) Mean ± SD/ Median (Q1, Q3)	Scrub Typhus (n=82) Mean ± SD/ Median (Q1, Q3)	P value
Haemoglobin (gm/dL)	14.93 ± 2.01	12.00 ± 2.24	0.000*
TLC (cells/µL)	4750 (3400,6900)	7700 (5875,11125)	0.000*
Platelet (cells/µL)	77500 (33000,126500)	113500 (64250,160750)	0.001*
Neutrophil (%)	51.8 ± 16.1	62.2 ± 16.5	0.000*
Lymphocyte (%)	53.9 (41.8, 64.4)	21.5 (16.4, 33.5)	0.005*
NLR	1.9 (1.0,3.0)	3.0 (1.6,4.3)	0.001*
Creatinine (mg/dL)	1.0 ± 0.3	1.1 ± 0.7	0.947
Sodium (meq/L)	136.41 ± 3.41	132.28 ± 5.09	0.000*
Potassium (meq/L)	4.25 ± 0.46	4.16 ± 0.63	0.298
Total bilirubin (mg/dL)	0.5 (0.4,0.8)	1.2 (0.7, 4.1)	0.000*
Direct bilirubin (mg/dL)	0.2 (0.1, 0.3)	0.7 (0.3, 3.5)	0.000*
AST (IU/L)	91 (52, 164)	90.5 (57.8, 161.3)	0.583
ALT (IU/L)	58 (36.5, 117)	80 (51.5, 121.5)	0.123
Total protein (gm/dL)	6.96 ± 0.59	6.33 ± 0.73	0.000*
Albumin (gm/dL)	4.03 ± 0.41	3.13 ± 2.98	0.000*
CRP (mg/dL)	8.58 (4.64, 26.32)	80.25 (45.13, 161.06)	0.000*

The mean duration of fever was 4.79 days and 7.25 days in Dengue and Scrub Typhus respectively. This was similar to what was observed by Mitra, *et al* where the mean duration was 5.9 days for Dengue and 8.1 days for Scrub Typhus[9]. In Dengue fever, the median hospital stay was 4 days, while in Scrub Typhus, it was 6 days. In our study, fever was the most common presenting symptom followed by myalgia in both the groups. In another study conducted by Laul, *et al* done in North India on Dengue, fever (100%) was the most common symptom followed by headache (87%)[10]. Bleeding manifestations were present in 3.7% of patients of Dengue infection. This contrasts with a previous study by Laul, *et al* where it was 21%[10]. Eschar was noted in 17.07% of patients with Scrub Typhus. Previous studies noted a much higher percentage, as observed in the study by Chang, *et al* in Taiwan, where it was 62.5% and in the study by Premraj, *et al* where eschar was present in 58% of cases[11,12].

Skin rash was present in 26.8% of Dengue patients whereas the study done in Vellore noted a skin rash in 14.2% of the patients[9]. 4.8% of Scrub Typhus patients also reported a skin rash. In our study, hypotension was noted in 9.7% of Scrub Typhus and 3.6% of Dengue patients. 40.2% of patients with Scrub Typhus had icterus, whereas only 4.8% of patients of Dengue had icterus.

Hepatomegaly was found to be more common in Scrub Typhus (18.2%) when compared to Dengue (7.3%), whereas Splenomegaly was more frequently noted in Dengue (9.7%) than Scrub Typhus (6%). As reviewed in an article by Zubair, *et al* the incidence of Hepatomegaly in adult patients with Dengue infection ranges from 4 to 52%[13]. The wide variations in the clinical manifestations observed in patients may be attributed to the differences in the age groups of the population affected along with the extent of severity of disease in them. Laboratory parameters such as haemoglobin, total protein, albumin, sodium, NLR, platelet, total bilirubin, and direct bilirubin values were statistically significant between the two groups. This was similar to what was observed by Mitra, *et al*[9]. However, our study found no significant difference of liver enzymes like ALT, AST between the two groups. The median CRP levels in Dengue was 8.58mg/dL and 80.25mg/dL in scrub typhus. Voung, *et al* noted a median CRP level of 30.2mg/dL in their study on Dengue whereas Kim HL, *et al* reported a mean CRP of 10.54 in their study of Scrub Typhus patients[14,15]. Hepatitis was noted in 63.4% of Scrub Typhus and 45.1% of Dengue patients. Another study by Griffith, *et al* in Vellore noted Hepatitis in 63.8% of cases[16].

Patients in the Scrub Typhus group had more complications, such as ARDS (23.1%), encephalitis (9.7%) and myocarditis (7.3%) when compared to Dengue (ARDS: 12.1%, encephalitis:1.2%, myocarditis: 12.2%). This could be attributed to the more complex pathogenesis of Scrub Typhus infection. Mortality was observed in the Scrub typhus group (n=1, 3.5%). The cause of mortality in the Scrub Typhus group was multi-organ dysfunction syndrome. In a study conducted by Patil, *et al* on Dengue infection, hepatitis was present in 33% of patients, and 3% had ARDS, while another 3% had encephalitis. The mortality rate was 3.2% in their study[17].

Few studies have observed the differences in clinical and laboratory features between these two illnesses. A study by Chang, *et al* in Taiwan showed significant differences in clinical features such as cough and eschar and the laboratory features showed that WBC count, platelet count, PT, APTT, BUN and creatinine were significantly different between the two groups[11].

A study done in Vellore by Mitra S, *et al* identified seven clinical variables based on multivariate analysis which included age, oxygen saturation, altered sensorium, haemoglobin, total leucocyte count, total bilirubin and AST values[9]. Six different scoring models were developed, and among them, model 2 exhibited a sensitivity of 84%. A cut off score of 13 was used. This model was however not validated. In our study, we devised a scoring model based on nine variables: age, haemoglobin, total leucocyte count, neutrophil-lymphocyte ratio, platelets, total bilirubin, CRP, albumin and altered sensorium. In this model, a total score of <4 suggests Dengue, and >4 suggests Scrub Typhus. When tested on a different group of patients, this scoring method had a sensitivity of 72% for patients with Dengue fever and 48% for patients with Scrub Typhus.

Very few studies have been undertaken to distinguish between these two most prevalent causes of acute febrile illness. Although certain features overlap, there are differences which can be incorporated to devise a model which can help differentiate the two at the time of presentation. Our study aimed to do the same.

Conclusion

Clinical features significant between the two infections were myalgia, arthralgia, breathlessness, altered sensorium, pulse rate, respiratory rate, temperature and hepatomegaly. Additionally, laboratory features such as hemoglobin, total leucocyte count, platelet, neutrophil-lymphocyte ratio, CRP, total bilirubin, and albumin were found to be significant between the two groups. When compared to Dengue fever, patients with Scrub Typhus had more complications such as ARDS, encephalitis and Myocarditis. A scoring model based on nine variables gave a cut off score of 4. A score of <4 suggested Dengue and >4 suggested Scrub Typhus. When validated, this score demonstrated a sensitivity of 72% for dengue and 48% for scrub typhus.

Limitation :

Logistic regression analysis would have given a better scoring model based on Odds Ratio but could not be used owing to the limited study population. The etiology for acute febrile illnesses is vast and this scoring model is limited only to Dengue and Scrub Typhus infections.

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Conflict of Interest : None.

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