ORIGINAL ARTICLE

Dengue Fever Scoring System: New Strategy for the Early Detection of Acute Dengue Virus Infection in Taiwan

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Background/Purpose: Dengue fever is an important public health problem in Southern Taiwan. The purpose of this study was to develop a dengue scoring system using a three-stage process, which may be used as a guidance tool for the early diagnosis of dengue fever.

Methods: A retrospective study was conducted to identify factors useful for the early diagnosis of dengue fever. We assessed the clinical and laboratory features of 89 adult patients with dengue from 2002 to 2004 at a community-based hospital. They were compared with 14 patients with scrub typhus, 104 with Q fever, and 35 with murine typhus, which might present similar symptoms and signs as dengue infection. A scoring system was designed after analysis of the retrospective study and with the assistance of 10 expert clinicians. For the second stage, we evaluated efficiency in differentiating dengue fever from Q fever, scrub typhus and murine typhus in three hospitals from 2002 to 2005. For the third stage, we prospectively used the dengue scoring system for 498 cases that clinically were suspected as having dengue infection in the city of Kaohsiung from January 2006 to September 2006.

Results: The performance of the scoring system was 88.1% sensitivity, 94.9% specificity, 95.7% positive predictive value (PPV), and 86.1% negative predictive value (NPV). Evaluation of the scoring system at the third stage revealed 90.7% sensitivity, 86.9% specificity, 81.4% PPV, and 93.6% NPV.

Conclusion: The dengue scoring system had a high NPV that might be helpful in the early diagnosis of dengue fever in adults before laboratory data are available. [*J Formos Med Assoc* 2009;108(11):879–885]

Key Words: dengue, murine typhus, Q fever, scoring system, scrub typhus

Dengue fever and rickettsial diseases are common infections in Asia and often present as an acute febrile illness of unclear etiology.[1,2] Many clinical manifestations and abnormalities in the laboratory results of dengue fever are found in other common infections, such as scrub typhus, murine typhus, or Q fever.[3] Therefore, early diagnosis of dengue fever is difficult.

There have been cases of dengue fever in Southern Taiwan since 1987.[4] However, the number of cases was not as high as in most other epidemic areas, thus the experience of clinicians in

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Taiwan diagnosing dengue infection has been somewhat limited. Our aims were to identify the differences among the characteristics of dengue fever and other endemic tropical diseases including scrub typhus, murine typhus and Q fever, and to develop a scoring system for the early detection of dengue infection and subsequent recognition of outbreaks. We present the processes involved in the development of a dengue scoring system, which was validated prospectively during a dengue outbreak in Taiwan in 2006.

Patients and Methods

In the first stage, we reviewed retrospectively cases of dengue fever, scrub typhus, murine typhus and Q fever to identify the distinguishing characteristics of dengue infection. Eighty-nine patients with serologically confirmed dengue infection who were admitted to Kaohsiung Municipal Hsiao-Kang Hospital during an epidemic from 2002 to 2004 were included. We reviewed also the charts of patients with scrub typhus, murine typhus, and Q fever, who were admitted to Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung Medical University Hospital, and National Chen Kung University Hospital between 1995 and 2005. Fourteen patients had scrub typhus, 104 had Q fever, and 35 had murine typhus. Data including demographic characteristics, clinical manifestations, and laboratory results were collected using a standard case record form.

We included only cases of adult dengue fever that were confirmed by serological or virological studies. Clinically suspected dengue fever was defined as the presence of fever and any two of the following symptoms: headache, retro-orbital pain, myalgia, polyarthralgia, skin rash, nausea and vomiting, or hemorrhagic manifestations.[5] Blood samples were drawn in the acute stage (within 7 days after the onset of symptoms) and during the convalescent stage (14–28 days after the onset of symptoms), and were sent to the Kaohsiung Branch Office, Center for Disease Control, Ministry of Health, Taiwan. The diagnosis of dengue fever was confirmed by meeting one of the following criteria: (1) virus isolation; (2) positive result of real-time polymerase chain reaction; (3) positive result of higher titer dengue-specific IgM and IgG antibody in a single serum specimen, in which cross-reaction to Japanese encephalitis had been excluded; or (4) positive seroconversion or ≥ 4-fold rise in dengue-specific IgM or IgG antibody from the acute phase compared with convalescent phase.

The diagnosis of dengue hemorrhagic fever (DHF) was based on the findings of hemoconcentration (increased hematocrit ≥ 20%), evidence of plasma leakage (ascites or pleural effusion), thrombocytopenia (platelet count ≤ 100,000/mm^3), and hemorrhagic manifestations. A rapid and weak pulse, narrowing of the pulse pressure to < 20 mmHg, or hypotension was used to establish the diagnosis of dengue shock syndrome.[1] The diagnosis of Q fever was made based on the presence of fever and a compatible serological profile, which required a ≥ 4-fold increase in phase II IgG titers between the acute and convalescent sera, or the presence of a significant titer of phase II IgM (≥ 1:50). The technique used for antibody detection was as previously described.[6] Scrub typhus was diagnosed if the indirect immunoperoxidase IgG antibody titers were ≥ 1:1600 or IgM titers were ≥ 1:400 in a single acute specimen, or if there was a ≥ 4-fold increase in the antibody titer between the acute and convalescent serum samples.[7] Endemic murine typhus was diagnosed if indirect immunoperoxidase IgG antibody titers were ≥ 1:1600 or IgM titers were ≥ 1:400 in a single acute specimen, or if there was a ≥ 4-fold increase in antibody titer between the acute and convalescent serum samples.[7]

Relative bradycardia is defined as an increase in heart rate of < 10 beats/minute for every 1 °C increase in temperature, in the absence of cardiac arrhythmia, pacemaker, or beta-blockers.[7,8] The laboratory data of the two groups were also compared and analyzed.

In the first stage, we compared the demographics and clinical and laboratory data between the 89 dengue cases and 153 rickettsial/Q fever

cases. The opinions of 10 clinicians (5 infectious disease and 5 primary care clinic doctors) were requested, to determine variables and their weighting for scoring systems that would be more easily accessible during clinical practice. The selected variables and weight of each variable was further examined for statistical significance using the receiver operating characteristic (ROC) curve to choose the best model. A dengue scoring system was designed using the above procedure.

For the second stage, we evaluated the efficiency in differentiating dengue fever from Q fever, scrub typhus, and murine typhus in three hospitals from 2002 to 2005.

For the third stage of this research, we used the dengue scoring system prospectively to assess the 498 clinically suspected cases of dengue fever during an epidemic in Kaohsiung from January 2006 to September 2006. These included 193 cases of confirmed dengue fever (2 of the 193 cases were DHF) and 305 non-dengue fever cases. We assessed the usefulness of the scoring system, not only in differentiating endemic rickettsial diseases plus Q fever, but also other non-dengue disease with similar symptoms to dengue infection.

Statistical analyses were performed using Fisher's exact test for categorical variables and the *t* test for continuous variables. Clinical and laboratory findings were compared using SPSS version 12.0 (SPSS, Chicago, IL, USA). The sensitivity and specificity of the model for predicting dengue infection among the first-stage study subjects were determined for each score value. Performance of the dengue scoring system was assessed using the ROC curve, and we calculated the area under the ROC curve for the prediction model.[9] The ROC curve analysis was performed by MedCalc version 9.3.2.0 (MedCalc Software, Mariakerke, Belgium).

Results

First stage

The clinical and laboratory parameters in the dengue and rickettsial/Q fever groups (including scrub typhus, murine typhus and Q fever) in the first stage of study are presented in Table 1. For the dengue fever group in 2002–2004, the mean age was 48.69 years, and 54 subjects (60.67%) were male (Table 1). For the rickettsial/Q fever group, the mean age was 49.51 years, and 123 subjects (80.39%) were male. Using a univariate analysis, a significantly higher proportion of the rickettsial and Q fever group were male.

Patients in both groups had low mean lymphocyte counts, but patients with dengue had significantly lower mean values for leukocyte and platelet counts. Patients with dengue also had significantly higher mean values for alanine aminotransferase (AST) than aspartate aminotransferase (ALT), but rickettsial/Q fever patients had significantly lower AST than ALT levels. A significantly higher proportion of these patients also had relative bradycardia. The clinical characteristics are noted in Table 1. These differed significantly between dengue and endemic rickettsial diseases and Q fever, and were included in the dengue scores after taking into consideration the opinions of the 10 clinicians. However, the scoring system was designed for early detection of dengue infection. Therefore, only clinical and epidemiological data were included as variables in the scoring system (Table 2). A ROC curve, which plotted the false-positive rate against the true-positive rate for each possible cut-off for a diagnostic test, had an area under the curve of 0.958 for the dengue scoring system (Figure). A perfect diagnostic test with 100% sensitivity and specificity would have an area under the curve of 1.0. The ROC curve derived from this model identified 6 as the ideal threshold for the dengue score, with a sensitivity of 87.64% [95% confidence interval (CI): 79.0–93.7%], and a specificity of 95.42% [95% CI: 90.8–98.1%).

Second stage

When using the dengue scoring system (Table 2) for 101 confirmed dengue and 78 rickettsial and Q fever diseases cases during 2002–2005 in the three hospitals, there were 89 cases of dengue fever and four of rickettsial infection or Q fever

Table 1. Comparison of demographics, initial clinical presentation and laboratory results between dengue fever and rickettsial/Q fever group*

Characteristics	Dengue fever ($n=89$)	Rickettsial/Q fever ($n=153$)	p
Demographic information			
Age (yr)	48.69 ± 17.40	49.51 ± 15.31	0.15
Male	54 (60.67)	123 (80.39)	0.001†
Initial clinical presentations			
Fever	86/89 (96.62)	147/153 (96.07)	1‡
Headache	62/86 (83.64)	74/107 (69.16)	0.657†
Skin rash	56/70 (80.00)	14/94 (14.89)	0.000†
No cough or rhinorrhea	38/66 (57.58)	49/69 (71.01)	0.103†
GI symptoms‖	42/74 (57.53)	51/99 (51.52)	0.494†
Bleeding sign	26/89 (29.21)	2/153 (1.31)	0.000‡
Relative bradycardia	7/46 (15.22)	80/101 (79.21)	0.000†
Fever before admission (d)	3.44 ± 1.94 (68)	7.27 ± 5.37 (129)	0.000§
Defervescence after admission (d)	1.52 ± 1.45 (62)	5.99 ± 6.47 (127)	0.000§
Total fever duration (d)	4.92 ± 4.92 (61)	14.23 ± 12.35 (131)	0.000§
Total admission length (d)	6.22 ± 1.87 (51)	8.80 ± 4.27 (56)	0.001§
Initial laboratory results			
WBC (/mm^3)	4120 ± 4110 (76)	7080 ± 3120 (146)	0.004§
Neutrophils (%)	58.04 ± 19.54 (35)	65.73 ± 13.02 (139)	0.055
Hemoglobin (g/dL)	14.23 ± 1.52 (76)	13.58 ± 13.58 (145)	0.175
Platelets (/mm^3)	62,380 ± 51,380 (75)	113,590 ± 77,610 (146)	0.000§
Lowest platelet count (/mm^3)	64,840 ± 60,540 (56)	157,850 ± 157,850 (33)	0.000§
AST (U/L)	128.03 ± 188.22 (74)	131.23 ± 164.11 (120)	0.589§
ALT (U/L)	92.81 ± 117.7 (74)	146.48 ± 154.74 (120)	0.000
AST > ALT †	59/73 (80.82)	59/147 (40.14)	0.000†
Blood urea nitrogen (mg/dL)	62 ± 4.50 (62)	14.21 ± 12.67 (132)	0.68
Serum creatinine (mg/dL)	1.49 ± 2.96 (63)	1.23 ± 1.06 (136)	0.205
Total bilirubin (mg/dL)	0.66 ± 0.644 (25)	1.9 ± 2.94 (121)	0.000§
Alkaline phosphatase (U/L)	152.43 ± 89.79 (23)	255.15 ± 272.54 (111)	0.019§
C-reactive protein (mg/L)	18.65 ± 20.05 (35)	83.54 ± 60.16 (111)	0.000§

**Data presented as n (%) or total confirmed cases/total reported cases (%) or mean ± standard deviation (total tested cases); † χ^2 test; ‡Fisher's exact test; §t test; ‖included poor appetite, abdominal pain, diarrhea and nausea. GI = gastrointestinal; WBC = white blood cell; AST = aspartate aminotransferase; ALT = alanine aminotransferase.*

with a score ≥ 6 points. Thus, such results represented a sensitivity of 88.12%, a specificity of 94.87%, a positive predictive value (PPV) of 95.7%, and a negative predictive value (NPV) of 86.05%.

Third stage

For stage 3, we used the dengue scoring system prospectively while there was an outbreak of dengue fever in Kaohsiung during 2006. There were 193 cases of dengue fever and 305 of clinically-suspected dengue fever that later had a negative laboratory result for dengue in an outbreak at Kaohsiung from January 2006 to September 2006. There were 175 patients with dengue fever and 40 without dengue fever who had a score of ≥ 6 points. The scoring system had a sensitivity of 90.67%, a specificity of 86.89%, a PPV of 81.4%, and an NPV of 93.63% for prediction of dengue fever among febrile patients. In the 305 cases of clinically suspected dengue fever that were later found to be negative by laboratory tests (non-dengue fever group), we found that the etiology of the non-dengue group included

Table 2. Proposed dengue scoring system

Characteristics	Score
(I) Epidemiology	
Recent travel to Southeast Asia or endemic dengue fever in Taiwan within 1 week	4
(II) Clinical symptom	
Skin rash	3
Bleeding sign*	3
Fever	2
Headache, retrobulbar pain, bone pain, myalgia	1
GI symptoms†	1
Absence of cough and rhinorrhea	1
(III) Differential diagnosis	
Fever > 7 days	–8
Identified infection focus (e.g. eschar of scrub typhus and upperrespiratory infection)	–10

**Included petechia, gum bleeding, epistaxis, gastrointestinal bleeding, hemoptysis, hematuria and menorrhagia; †included poor appetite, abdominal pain, diarrhea and nausea.*

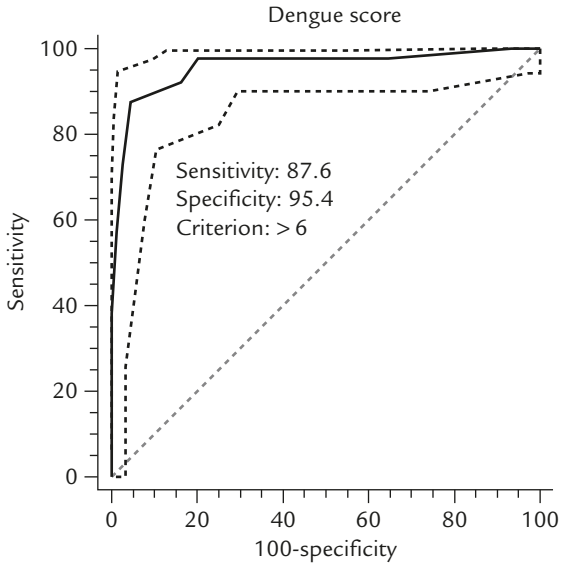

Figure. Receiver operating characteristic curve for dengue scoring system. The dotted lines indicate the 95% confidence interval.

the following: influenza virus infection ($n=1$), Epstein–Barr virus infection ($n=1$), human immunodeficiency virus infection ($n=1$), chickenpox ($n=2$), mycoplasma pneumonia ($n=3$), scrub typhus ($n=3$), murine typhus ($n=1$), malaria ($n=1$), and Q fever ($n=1$). No pathogen was identified among the patients in non-dengue group.

Discussion

The early symptom complex of acute dengue virus infection is protean and it is difficult to distinguish it from other kinds of febrile illnesses.[10–12] There are imported and indigenous dengue fever cases in Kaohsiung every year.[13] Moreover, scrub typhus or Q fever[14] are the two frequently listed presumptive diagnoses in patients who present with fever of unknown etiology in Southern Taiwan.[7] Dengue fever, rickettsial diseases and Q fever have similar laboratory data, making it difficult to diagnose dengue definitively. To confront the confusion in clinical diagnosis, the parameters of relative bradycardia and higher AST than ALT levels can be used for differentiating between these two types of fever (Table 1). The presence of relative bradycardia favors rickettsial disease,[8] whereas higher AST than ALT favors dengue fever (Table 1). The results in Table 1 show some laboratory data characteristics that are helpful when differentiating dengue from other diseases. However, the dengue scoring system decided on by experts favored clinical parameters (Table 2). Although this results in the loss of the usefulness of laboratory data in differential diagnosis, it might be feasible practically for clinicians to make an early diagnosis and grade the possibility of a diagnosis of dengue infection.

Not all physicians have experience in diagnosing dengue fever. If the index case is not reported, it is difficult for less-experienced physicians to detect dengue fever early. The sooner dengue is diagnosed, the sooner treatment can be administered, and the chances of recovery are increased significantly. Therefore, a scoring system is urgently needed that can differentiate dengue from other febrile patients in the emergency room or clinic. Our results, with regards to stage two of our study, revealed the differentiation power between

Table 3. The validity of the dengue scoring system with 101 cases of dengue infection and 78 cases of rickettsial infections/Q fever*

Cases	Dengue score	
	≥6	<6
Dengue fever	89	12
Rickettsial/Q fever	4	74
Subtotal	93	86

**Sensitivity = 88.1%; specificity = 94.9%; positive predictive value = 95.7%; negative predictive value = 86.1%.*

Table 4. Comparison of 193 cases of dengue fever with 305 cases of clinically suspected dengue fever, but negative results, in an outbreak in Kaohsiung from January 2006 to September 2006 using dengue score system

Cases	Dengue score	
	≥6	<6
Dengue fever	175	18
Suspected dengue fever but negative results	40	265

Sensitivity = 90.7%; specificity = 86.9%; positive predictive value = 81.4%; negative predictive value = 93.6%.

dengue and other endemic tropical diseases. This can help physicians and public health workers to detect dengue fever cases earlier. The appropriate treatment and public health measures can be initiated subsequently. The initial evaluation of suspected cases can guide public health workers in their control of dengue fever more specifically and efficiently. For example, better early diagnosis of dengue can enhance the efficacy to prevent dengue spread. Better recognition of the very unlikely cases might be able to reduce unnecessary insecticide spraying, which is labor-intensive, costly, and can lead to drug resistance. The cost-effectiveness of applying the dengue scoring system in public health requires validation by further study.

Data collection of patients from different hospitals, especially referrals from other medical centers, with retrospective designation could introduce potential bias into the specificity and sensitivity of the dengue scoring systems. To solve this problem, we collected prospectively the data for all the patients suspected of having dengue fever during the outbreak in Kaohsiung in 2006. Using the dengue scoring system, the sensitivity and specificity were both higher than 85% and there was a good NPV (93.63%) in stage 3 of the study (Table 4). This implies that the scoring system can be used prospectively in cases of clinically suspected dengue fever.

There is a possibility of inaccuracy in our scoring system. Dengue fever and rickettsial diseases may coexist. Thus, Table 2 should be used cautiously, especially for patients with atypical dengue fever symptoms and in concurrent endemic areas for dengue and rickettsial diseases. Dengue fever and rickettsial infections have similar clinical presentations and laboratory data; therefore, we found that it was more difficult to distinguish dengue fever from rickettsial diseases and Q fever (stage 2) than to distinguish dengue fever from all non-dengue fever cases (stage 3). Thus, the results of sensitivity and NPV in Table 3 were lower than the sensitivity in Table 4. Lastly, the hospitals in our study are referral hospitals. When patients went to these hospitals, they might have already been suffering from later stages of dengue fever. Their dengue scores would have been higher in these hospitals than in the clinics. However, cases included in the third stage of the study were not only in the referral center, but some were from local clinics. The non-dengue group includes many diseases, and not simply rickettsial diseases and Q fever. Therefore, the results of stage 3 (Table 4) indicate that the scoring system can be used in clinical practice.

Our study has the following limitations: (1) only adult cases were checked, and this potentially limits the ability to generalize the results to other countries where a large number of pediatric patients have dengue fever; and (2) in Taiwan, primary dengue infection is the major problem, whereas in Southeast Asian countries, such as Vietnam, secondary infections are the main problem. Further studies are needed if we wish to use these tables in other areas.

In summary, dengue fever is a public health threat each year in Taiwan. Early detection and prompt control are the two main pillars for successful infectious disease control. Clinicians can play an important role in the early diagnosis of dengue patients, and help public health workers to conduct the appropriate control measures at an earlier stage. This simple scoring system could be useful in the diagnosis of dengue infection by less-experienced physicians and public health workers, especially when rapid diagnostic tests are not available. Thus, dengue fever can be recognized early, which allows appropriate therapy and prevention strategies to be implemented.

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References

1. Pickard AL, McDaniel P, Miller RS, et al. A study of febrile illnesses on the Thai-Myanmar border: predictive factors of rickettsioses. *Southeast Asian J Trop Med Public Health* 2004;35:657–63.
2. Watt G, Jongsakul K, Chouriyagune C, et al. Differentiating dengue virus infection from scrub typhus in Thai adults with fever. *Am J Trop Med Hyg* 2003;68:536–8.
3. Chadwick D, Arch B, Wilder-Smith A, et al. Distinguishing dengue fever from other infections on the basis of simple clinical and laboratory features: application of logistic regression analysis. *J Clin Virol* 2006;35:147–53.
4. Lee MS, Hwang KP, Chen TC, et al. Clinical characteristics of dengue and dengue hemorrhagic fever in a medical center of southern Taiwan during the 2002 epidemic. *J Microbiol Immunol Infect* 2006;39:121–9.
5. Lai PC, Lee SS, Kao CH, et al. Characteristics of a dengue hemorrhagic fever outbreak in 2001 in Kaohsiung. *J Microbiol Immunol Infect* 2004;37:266–70.
6. Ko WC, Liu JW, Chuang YC. Acute Q fever as a cause of acute febrile illness of unknown origin in Taiwan: report of seven cases. *J Formos Med Assoc* 1997;96:295–7.
7. Cobelens FG, Groen J, Osterhaus AD, et al. Incidence and risk factors of probable dengue virus infection among Dutch travellers to Asia. *Trop Med Int Health* 2002;7:331–8.
8. Aronoff DM, Watt G. Prevalence of relative bradycardia in *Orientia tsutsugamushi* infection. *Am J Trop Med Hyg* 2003;68:477–9.
9. Centor RM, Schwartz JS. An evaluation of methods for estimating the area under the receiver operating characteristic (ROC) curve. *Med Decis Making* 1985;5:149–56.
10. Halstead SB. More dengue, more questions. *Emerg Infect Dis* 2005;11:740–1.
11. Viral haemorrhagic fevers. *Br Med J* 1975;4:67–8. [Editorial]
12. Wilder-Smith A, Schwartz E. Dengue in travelers. *N Engl J Med* 2005;353:924–32.
13. Tung YC, Lin KH, Chang K, et al. Phylogenetic study of dengue-3 virus in Taiwan with sequence analysis of the core gene. *Kaohsiung J Med Sci* 2008;24:55–62.
14. Chang K, Yan JJ, Lee HC, et al. Acute hepatitis with or without jaundice: a predominant presentation of acute Q fever in southern Taiwan. *J Microbiol Immunol Infect* 2004;37:103–8.