Validation of Probability Equation and Decision Tree in Predicting Subsequent Dengue Hemorrhagic Fever in Adult Dengue Inpatients in Singapore

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Abstract. We developed a probability equation and a decision tree from 1,973 predominantly dengue serotype 1 hospitalized adult dengue patients in 2004 to predict progression to dengue hemorrhagic fever (DHF), applied in our clinic since March 2007. The parameters predicting DHF were clinical bleeding, high serum urea, low serum protein, and low lymphocyte proportion. This study validated these in a predominantly dengue serotype 2 cohort in 2007. The 1,017 adult dengue patients admitted to Tan Tock Seng Hospital, Singapore had a median age of 35 years. Of 933 patients without DHF on admission, 131 progressed to DHF. The probability equation predicted DHF with a sensitivity (Sn) of 94%, specificity (Sp) 17%, positive predictive value (PPV) 16%, and negative predictive value (NPV) 94%. The decision tree predicted DHF with a Sn of 99%, Sp 12%, PPV 16%, and NPV 99%. Both tools performed well despite a switch in predominant dengue serotypes.

INTRODUCTION

Dengue is an important arthropod-borne disease affecting millions of people in tropical and subtropical regions. Of the wide range of disease severity, dengue hemorrhagic fever (DHF) is a more severe form that can present with case fatality rates as high as 16.6% if not given appropriate clinical management.¹ However, with optimal case management, death from dengue shock syndrome ranged from 1% to 5%, and could be as low as < 0.2%.² Early recognition of DHF is therefore critical in patient care. Previously published predictors for DHF included dengue serotype 2,^{3,4} Asian genotype,⁵ prior dengue infections,⁶ children,^{7,8} and white females.⁹

From 2004 to 2005, Singapore experienced the largest dengue epidemic to date. Over 9,459 and 14,200 cases were notified to our local healthcare system during each year, of which 8,154 (86.2%) and 12,510 (88.1%), respectively, were adults.^{10,11} The inability to differentiate progressors from non-progressors to severe disease led to 85% hospital admission that overwhelmed routine healthcare delivery. Reliable tools to predict subsequent development of DHF at the time of the first presentation to a health center remain a challenge.^{12–15} However, studies are limited to a specific time frame and none assessed the validity across different time periods. On the basis of the 2004 adult hospitalized cohort, we developed a probability equation to predict subsequent development of DHF upon presentation to the hospital. That probability equation had a sensitivity (Sn) of 98%, specificity (Sp) 60%, positive predictive value (PPV) 10%, and negative predictive value (NPV) 99%.¹⁶ To simplify the tool, we developed a decision tree that does not require computational calculations. The decision tree was found to have a Sn of 100%, Sp 46%, PPV 8%, and NPV 100%.¹⁷

A switch of predominant serotype to Dengue 2 in 2007 caused a resurgence of dengue epidemic in Singapore. To validate our predictive tools across different dengue serotypes, we evaluated the performance of these two predictive tools developed from our 2004 hospitalized adult dengue cohort in

our 2007 cohort, with different dominant serotypes of dengue, namely dengue 1 and dengue 2, respectively.¹⁸

MATERIALS AND METHODS

We collected demographic, epidemiologic, serial clinical, laboratory and radiological, treatment and outcome data for hospitalized dengue patients at Tan Tock Seng Hospital managed by the Department of Infectious Diseases with a standardized clinical care path in the years 2004 and 2007, with 1,973 and 1,017 cases in each cohort, respectively. Data were obtained from specialist outpatient clinic notes and from inpatient charts to cover the entire clinical course. According to World Health Organization (WHO) 1997 criteria, dengue fever (DF) is defined as reported fever or measured temperature of > 38°C with any two of the following manifestations: headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations, or leukopenia.¹⁹ Probable cases had positive acute dengue serology, as measured by the Dengue Duo IgM and IgG Rapid Strip Test (Panbio, Qld, Australia)^{20,21} and confirmed cases had positive dengue polymerase chain reaction (PCR) assay.²² Dengue hemorrhagic fever was diagnosed when all four criteria of fever, thrombocytopenia $\leq 100 \times 10^9/L$, hemorrhagic manifestations, and plasma leakage (hypoproteinemia, $\geq 20\%$ change in hematocrit, or pleural effusion or ascites) were present.¹⁹ Dengue shock syndrome (DSS) is defined as DHF and tachycardia $> 100/min$ or narrow pulse pressure < 20 mmHg, or DHF and systolic blood pressure < 90 mmHg.¹⁹ We further applied the WHO 2009 guideline on patients classified as having warning signs, if they had abdominal pain or tenderness, persistent vomiting ≥ 2 days, clinical fluid accumulation, mucosal bleeding, lethargy or restlessness, hepatomegaly, or hematocrit $> 50\%$ and platelet $< 20 \times 10^9/L$.²³

The two predictive tools for DHF were derived from comparing hospitalized adult dengue patients in 2004 from Tan Tock Seng Hospital, Singapore upon admission to predict any progression to DHF, as a guide for doctors in admitting patients presenting with dengue. A probability equation was derived from multivariate analysis with a cutoff point to minimize missing DHF, and comprised four variables: bleeding, serum urea, protein, and lymphocyte proportion.¹⁶ A decision

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tree was also derived from the same data using the χ^2 automatic interaction detector (CHAID) with bi-way and multi-way splitting, with resultant trees pruned for highest sensitivity with the shortest tree. The decision tree comprised three nodes: bleeding, serum urea, and protein.¹⁷

Patients with suspected dengue were referred to our specialist outpatient clinic, where they had blood collection for dengue and other relevant diagnostic tests, full blood count, serum protein and urea, and alanine and aspartate transaminases. They would be reviewed by our doctors when the blood results became available within 2 hours on the same day.

For the determination of the final diagnosis of DF, DHF, DSS and presence of warning signs, clinical and laboratory data from the entire clinical course were used. However, for the input variables for the probability equation and the decision tree, clinical bleeding was determined from illness onset to the time of presentation, and the results of lymphocyte proportion, serum protein, and urea on the day of presentation were used. For the probability equation, the values of lymphocyte proportion, serum protein, and urea as reported by the laboratory were entered into a computer program. For the decision tree, the cutoff values of serum urea > 4 mmol/L and serum protein < 67 g/L were used.¹⁷ Because these two predictive tools were designed to predict development of DHF after hospitalization, we did not evaluate their performance in relation to WHO 2009 warning signs or severe dengue.

Statistical methods. To compare cases in the 2004 and 2007 cohorts, Fisher's exact test was used to compare categorical variables from the two cohorts and Mann-Whitney *U* test to compare the continuous variables with non-normal distribution. The analysis was performed in SPSS version 16 (SPSS Inc., Chicago, IL), with the level of significance set at a two-tailed *P* value of < 0.05. Sensitivity, specificity, PPV, NPV of the two predictive tools developed from the 2004 cohort was computed for the 2007 cohort.

RESULTS

Patient characteristics. The median age of the 2004 cohort was 32.0 years (5th–95th percentile, 17–58 years) and the 2007 cohort was 35.0 years (5th–95th percentile, 19–61 years); males predominated in both cohorts. Less than half of the subjects (917 of the 2004 cohort [46.5%] and 318 of the 2007 cohort [31.3%]) were dengue confirmed by PCR and all of the remaining subjects were serology positive. Compared with 2004, the 2007 cohort had more co-morbid conditions (7.3% versus 18.3%, *P* < 0.001) (Table 1).

Among the 1973 hospitalized dengue patients from 2004, 1855 (94.0%) had DF and 118 (6.0%) had DHF of which 82 (4.2%) progressed to DHF from DF after admission. In 2007, of 1,017 adult dengue patients admitted to our hospital, 802 (78.9%) had DF and 215 (21.1%) had DHF of which 131 (12.8%) progressed to DHF from DF after hospital admission. Fatal outcomes occurred in 1 and 3 patients from 2004 and 2007 cohorts, respectively. Apart from leukopenia (78.9% versus 70.8%), other criteria for probable dengue (headache [35.1% versus 55.7%], retro-orbital pain [0.4% versus 2.6%], myalgia/arthralgia [71.1% versus 77.2%], rash [52.2% versus 66.6%], and hemorrhagic manifestations [7.3% versus 65.3%]) were more common in the 2007 cohort. The difference in clinical presentation for probable dengue and DHF were statistically significant between the two cohorts

(*P* < 0.001). Of note, 623 (31.6%) in the 2004 cohort and 784 (77.1%) in the 2007 cohort had any warning signs (*P* < 0.001). Details of the clinical presentations are shown in Table 1.

In 2004, the patients presented at a median of 5 days versus 6 days in 2007 from illness onset (*P* < 0.001). There was more intravenous fluid administration in 2007 compared with 2004 (90.4% versus 57.6%) but fewer patients received platelet transfusion (7.0% versus 12.6%) (*P* < 0.001).

Validation of DHF predictive tools. In the 2007 cohort, the probability equation had a Sn of 94%, Sp 17%, PPV 16%, and NPV 99% for the entire cohort, whereas the decision tree had a Sn 99%, Sp 12%, PPV 16%, and NPV 99% in predicting DHF. Compared with their performances in the 2004 cohort, both tools had comparable Sn and NPV, but lower Sp in the 2007 cohort (Table 2). When we analyzed for subgroups of PCR-confirmed and serology positive cases in the 2007 cohort, PCR-confirmed cases showed higher Sn ([97% versus 92%] and [100% versus 99%]) and lower Sp ([14% versus 17%] and [10% versus 13%]) by the probability equation and decision tree, respectively, compared with serology positive cases.

DISCUSSION

We showed comparable performance in identifying post-admission development of DHF in our 2007 cohort with a different circulating predominant dengue serotype, especially in our PCR-confirmed subgroup. In addition, for the 2007 cohort, compared with serology positive cases, the tools performed better in PCR-confirmed cases. The PCR-positive cases were early presenters during the febrile viremic phase.²² Although other studies have reported different methods to predict DHF, our study has now validated our predictive tools using different cohorts with different dominant serotypes. Of importance, our predictive tools were intended not to miss a case of DHF, and the high sensitivity and negative predictive value in the validation cohort confirmed the use of the probability equation and decision tool.

Our 2007 hospitalized adult dengue cohort appeared to have higher incidence of DHF and warning signs for severe dengue. The reasons for this may include the application of these two predictive tools in guiding hospital admission at our hospital since March 2007. Clinicians can better predict the development of DHF at the time of presentation and avoid unnecessary hospitalizations. As a result, potentially more severe cases were admitted to the hospital resulting in more DHF in the 2007 cohort. Differences in interaction between host and different virus serotypes may also play an important role. In the 2007 cohort, the dominant dengue serotype was dengue 2, which tends to cause more severe disease.^{3,4,16} In addition, a new cosmopolitan genotype was observed in dengue 2.¹⁸ Interestingly, the emergence of this cosmopolitan genotype among Dengue 2 has been reported in India²⁴ and the Philippines.²⁵ Although there has been no study that correlated increased viral transmission or virulence with the cosmopolitan genotype, several studies reported increased viral replication with different dengue 2 genotypes. In Vietnam, Dengue 2 Asian genotype was associated with higher viremia in pediatric patients compared with Asian/American genotype.²⁶ In a humanized mouse model, Dengue 2 Southeast Asian genotype produced greater viremia and thrombocytopenia and more rash than Indian and West African genotypes.²⁷ In mosquitoes, the Dengue 2 Southeast Asian genotype achieved higher viremia

TABLE 1
Comparison of demographic, epidemiologic, clinical, and laboratory features of 2004 and 2007 cohorts

	Year 2004 (N = 1973)		Year 2007 (N = 1017)		P value
Demographic and epidemiologic data					
Median age, years (5th–95th percentile)	32.0 (17.0–57.4)		35.0 (19.0–61.0)		< 0.001*
Male	1256	(63.7%)	666	(65.5%)	0.334
Any co-morbidity	145	(7.3%)	186	(18.3%)	< 0.001
PCR positive cases	917	(46.5%)	318	(31.3%)	< 0.001
Median duration of illness at presentation, days (range)	5 (1–16)		6 (1–31)		< 0.001*
WHO criteria					
Dengue fever	1855	(94.0%)	802	(78.9%)	< 0.001
Fever symptom	1855	(100.0%)	802	(100.0%)	< 0.001
Headache	651	(35.1%)	447	(55.7%)	< 0.001
Eye pain	7	(0.4%)	21	(2.6%)	< 0.001
Myalgia/arthritis	1318	(71.1%)	619	(77.2%)	0.001
Rash	969	(52.2%)	534	(66.6%)	< 0.001
Any bleeding	135	(7.3%)	524	(65.3%)	< 0.001
Leukopenia	1463	(78.9%)	568	(70.8%)	< 0.001
Dengue hemorrhagic fever	118	(6.0%)	215	(21.1%)	< 0.001
Plasma leakage					
(1) Hematocrit change ≥ 20%	30	(25.4%)	36	(16.7%)	0.0623
(2) Pleural effusion or ascites	3	(2.5%)	37	(17.2%)	< 0.001
(3) Hypoproteinemia	105	(89.0%)	127	(59.1%)	< 0.001
Any warning signs	623	(31.6%)	784	(77.1%)	< 0.001
Abdominal pain or tenderness	338	(54.3%)	398	(50.8%)	0.200
Persistent vomiting ≥ 2 days	71	(11.4%)	124	(15.8%)	0.020
Clinical fluid accumulation	13	(2.1%)	97	(12.4%)	< 0.001
Mucosal bleeding	249	(40.0%)	376	(48.0%)	0.003
Lethargy or restlessness	na	na	362	(46.2%)	na
Hepatomegaly	0	(0%)	30	(3.8%)	< 0.001
Hematocrit > 50% and platelet < 20 × 10 ⁹ /L	61	(9.8%)	58	(7.4%)	0.1123
Other clinical and laboratory features					
Altered mental status (encephalopathy)	5	(0.3%)	3	(0.3%)	> 0.99
AST ≥ 1000 units/Liter	31	(1.6%)	7	(0.7%)	0.056
Serum creatinine > 2 × ULN	7	(0.4%)	11	(1.1%)	0.024
ICU admission	7	(0.4%)	6	(0.6%)	0.385
Blood transfusion	1	(0.1%)	8	(0.8%)	0.001
Intravenous fluid	1136	(57.6%)	919	(90.4%)	< 0.001
Platelet transfusion	249	(12.6%)	71	(7.0%)	< 0.001
Mean† length of hospital stay, days (range)	4.1 (1–22)		3.8 (1–25)		< 0.001*
Death	1	(0.1%)	3	(0.3%)	0.117

* Mann-Whitney U test.

† Geometric mean.

Variables shown are all from the whole hospitalization unless otherwise stated, and are numbers with percentage in parentheses unless otherwise stated.

PCR = polymerase chain reaction; WHO = World Health Organization; AST = aspartate transaminase; ULN = upper limit of normal; ICU = intensive care unit; na = not available.

P values were determined by Fisher's exact test unless otherwise stated.

in midgut and earlier viral replication in salivary glands compared with American genotype.²⁸ Whether the cosmopolitan genotype possesses this similar quality should be further investigated in mosquitoes and humans.

TABLE 2

Validation of the probability equation and decision tree in the 2007 cohort for predicting progression to dengue hemorrhagic fever

	Sn (%)	Sp (%)	PPV (%)	NPV (%)
Probability equation				
2004* Cohort	98	60	10	99
2007† (the whole cohort)	94	17	16	94
2007 (PCR positive only)	97	14	22	94
2007 (serology positive only)	92	17	13	94
Decision tree				
2004* Cohort	100	46	8	100
2007† (the whole cohort)	99	12	16	99
2007 (PCR positive only)	100	10	22	100
2007 (serology positive only)	99	13	13	99

* 82 (31 [PCR], 51 [serology]) out of 1937 (893 [PCR], 1044 [serology]) patients progressed to DHF.

† 131 (56 [PCR], 75 [serology]) out of 933 (295 [PCR], 638 [serology]) patients progressed to DHF.

Sn = sensitivity; Sp = specificity; PPV = positive predictive value; NPV = negative predictive value; PCR = polymerase chain reaction; DHF = dengue hemorrhagic fever.

Our study is limited by the fact that no dengue serotype data were available for individual study subjects. Because Tan Tock Seng Hospital is a major infectious disease center in Singapore, which provided care for ~40% of all reported dengue patients in Singapore in 2005,¹⁸ and our cohort sizes were large, it is probable that the predominant dengue serotype in our cohorts may mirror national data where the predominant serotype was dengue 1 in 2004 and dengue 2 in 2007.¹⁸ In addition, our derivation and validation cohorts were both dengue patients presenting to and managed at a hospital. In a prospective adult dengue study at primary care in Singapore, 2 of 133 patients subsequently developed DHF²⁹. Notably, three of the four parameters in our probability equation were laboratory test results, which may not be easily available in resource-poor countries where dengue and DHF may have a high public health impact.

In conclusion, our study showed that three to four simple clinical and laboratory markers (namely bleeding, serum urea and protein, and lymphocyte proportion) had high sensitivity (92–100%) for predicting subsequent DHF, and a high negative predictive value (94–100%) in ruling out DHF in adult dengue patients presenting to the hospital in Singapore. The

advantage of the decision tree over the probability equation is its simple application in clinical practice. The tools can assist clinicians in deciding between hospitalization and outpatient monitoring of adult dengue patients.

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