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Predicting severe dengue using quantified warning signs. A retrospective cohort study

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ABSTRACT

Objective: To develop and evaluate predictive models by quantifying warning signs prior to the development of severe dengue.

Methods: A retrospective cohort study was conducted in which the total number of warning signs each day was compared between dengue with warning signs and severe dengue. Multivariate logistic regression with forward likelihood ratio method was employed to achieve the best fit models for the prediction of severe dengue. The models were also being explored by adding diarrhoea and removing lethargy. Receiver operating characteristics were then used in these best fit models to identify suitable cut-off probability values derived from the equation of the models.

Results: Median age of patients was 26 years old (interquartile range was 15 years) and 65.3% (1110) were males. Age with total number of warning signs at day one of illness (model T1) and age with total number of warning signs at day two of illness (model T2) were identified as the best fit models. The best probability cut-offs for model T1 was 0.0506 with 10.1% positive predictive value, 96.4% negative predictive value, 99.4% sensitivity, 1.8% specificity; for model T2 was 0.0503 with 10.2% positive predictive value, 96.4% negative predictive value, 99.4% sensitivity, 1.8% specificity.

Conclusions: The models developed in this study might not reduce the burden effectively. Clinicians may use the models but the models must be re-validated in their clinical settings as the effect size might vary. Furthermore, the risk and benefit in selecting the cut-off values should be evaluated before implementing such models.

1. Introduction

More than 2.5 billion people, who constitute 40% of the world population, are at risk to the exposure of dengue infection. World Health Organization (WHO) estimated 50 to 100 million dengue infections occur annually. Thus, estimated 500 000 people with severe dengue require hospitalization each year and about 2.5% of those affected die[1].

Dengue clinical manifestation is divided into three phases: febrile, critical and recovery phase. Critical phase is the most important phase where the patient can either recover or die from the disease[2-4]. Unfortunately, critical phase is difficult to predict even with the new WHO classification which has a list of warning signs that warrants the admission of patients[5,6]. This led to unnecessary admission and in turn increased the health care burden due to the lack of specificity

of warning signs[7].

A better predictive model should be developed to overcome the burden of the disease. Furthermore, current treatment has not been able to cure the disease[8]. Hence, this study aimed to develop and evaluate predictive models by quantifying warning signs prior to the development of severe dengue.

2. Materials and methods

2.1. Study protocol

A retrospective cohort study was conducted to compare the quantified warning signs in severe dengue and dengue with warning signs. The warning signs were quantified by calculating the total number of warning signs developed each day prior to the development of severe dengue. The clinical classification of dengue infection was based on the dengue guidelines published by WHO[5].

All eligible medical records of patients who were admitted to Ampang Hospital from January to September 2014 were included in the study. All the medical records obtained from the census book in

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the Emergency Department were dengue cases requiring admission.

The patients included in the study were either dengue immunoglobulin M (IgM) or NS1 antigen positive, dengue IgM and NS1 antigen positive, with clinical diagnosis of dengue with warning signs or severe dengue (or its complication entity: severe plasma leakage leading to shock or fluid accumulation with respiratory distress, severe bleeding as evaluated by clinician and severe organ involvement). Dengue IgM results were obtained from the laboratory results of the hospital by tracing the medical records. NS1 antigen test results were obtained from the doctor's clerking of the patients' medical records as this test was performed at the Emergency Department by using rapid test kit. NS1 antigen positive results were included even though the dengue IgM test was negative because dengue IgM test can be negative if it was tested too early in the course of the disease. The clinical diagnoses were verified by using the classification guidelines[5].

The patients excluded from the study were patients with haematological or any other malignancy. The change in platelet count was one of the warning signs and hence malignancy was excluded as the platelet count may be altered due to the disease or chemotherapy treatment.

2.2. Statistical analysis

The data from the medical records from January 2014 until September 2014 were analysed. The demography (age, gender and race/nationality), the patients' pregnancy status and clinical diagnoses, the day of the severe dengue diagnosis made were described. Bar charts of the warning signs of each day were presented. Missing data were presented and excluded from the analysis due to a small percentage which might not alter the statistical analysis.

Binary logistic regression was used to analyse the predictor variables (age, gender, race/nationality and total number of warning signs of a particular day) and outcome variable (dengue with warning signs and severe dengue). In the univariate analysis, the detailed results were presented only if the omnibus test of the models was statistically significant. Forward likelihood ratio (LR) method was employed to achieve the best fit model for prediction. The variables included in the total number of warning signs were persistent vomiting, abdominal pain or tenderness, clinical fluid accumulation, mucosal bleed, liver enlargement, increase in haematocrit (HCT), decrease in platelet count and lethargy (first model). Although diarrhoea was not stated as a warning sign of dengue, the inclusion of diarrhoea into the second model was justified by the high frequency of the symptom among the patients recruited. Subsequently, lethargy was omitted from the second model to compare among the models. Lethargy was deemed as an unreliable sign due to the subjectivity of interpretation by the patients[9].

The analysis was performed according to each day of illness where warning signs developed before the diagnosis of severe dengue being made. This was to ensure the prediction was according to the days of illness prior to the development of severe dengue. The analysis was performed from day one to day five of illness since the frequency of severe dengue developed after day six was less than 10.2%. A *P*-value less than 0.05 (*P* < 0.05) was considered as statistically significant. SPSS version20 was used in the analysis.

The selection of the best predictive model was based on the best, improved Nagelkerke R square. The equation of the model yields odds which was then converted into probability (*p*) that was used in the receiver operating characteristics (ROC) to calculate the area under the curve (AUC), sensitivity (SENS), specificity (SPEC), positive predictive value (PPV) and negative predictive value (NPV) of two cut-offs (highest PPV and NPV). The *p* was calculated by the formula: $p = e^{\text{odds}} / (e^{\text{odds}} + 1)$, with 'e' as exponential.

3. Results

The median age of the patients was 26 years old with interquartile range (IQR) of 15 years old. Male patients were more than female with 1110 (65.3%) and 590 (34.7%), respectively. Comparison of the patients' demography and pregnancy status between dengue with warning signs and severe dengue was shown in Table 1. There were 130 (7.7%) missing data (warning signs only) of the 1700 patients recruited.

Table 1

Comparison of the patients' demography and pregnancy status between dengue with warning signs and severe dengue.

Demographic character		Median (IQR) or number of cases (%)	
		Dengue with warning signs	Severe dengue
Age (years)		26.0 (14.0)	24.0 (13.0)
Gender	Male	1009 (90.2)	101 (9.1)
	Female	520 (88.1)	70 (11.9)
Race (Malaysians)	Malay	865 (89.5)	101 (10.5)
	Chinese	221 (91.3)	21 (8.7)
	Indian	59 (90.8)	6 (9.2)
	Other Malaysians	11 (91.7)	1 (8.3)
Nationality (Non-Malaysian)	Bangladesh	123 (93.2)	9 (6.8)
	Myanmar	53 (85.5)	9 (14.5)
	Nepal	55 (94.8)	3 (5.2)
	Pakistan	47 (90.4)	5 (9.6)
	Indonesia	29 (72.5)	11 (27.5)
	India	23 (100.0)	0 (0.0)
	Iran	11 (84.6)	2 (15.4)
	Vietnam	7 (77.8)	2 (22.2)
	China	7 (100.0)	0 (0.0)
	Afghanistan	6 (100.0)	0 (0.0)
	Korea	4 (80.0)	1 (20.0)
	Thailand	2 (100.0)	0 (0.0)
	Sri Lanka	1 (100.0)	0 (0.0)
Pregnant	Philippines	1 (100.0)	0 (0.0)
	Congo	1 (100.0)	0 (0.0)
	Libya	1 (100.0)	0 (0.0)
	Syria	1 (100.0)	0 (0.0)
	Taiwan	1 (100.0)	0 (0.0)
		2 (40.0)	3 (60.0)

The number of patients who were diagnosed with severe dengue was 171 (10.1%) and out of which 24 (14.0%) of them did not develop any warning signs. Vomiting has the highest frequency in all first six days of illness and followed by diarrhoea in the first four days. At day five of illness, the second highest symptom was abdominal pain or tenderness. However, laboratory results of reduced platelet and increase in haematocrit level was the second highest at day six of illness. Figures 1–6 display the frequency of the warning signs in each day of illness among the patients from day one to day six of illness.

Among the severe dengue cases, 159 (93%) developed shock (decompensated or compensated shock), five (2.9%) myocarditis, three (1.8%) respiratory distress due to fluid accumulation (pleural effusion alone or with ascites), two (1.2%) shock and myocarditis, one (0.6%) severe bleeding and one (0.6%) severe bleeding and myocarditis. Only one patient died due to complication of shock. The mean (SD) day of severe dengue diagnosis being made was 5.2 (0.1) days with the range of 2 to 10 days.

In the univariate analysis, all except age, total number of warning signs at day one of illness without diarrhoea (T1) and with diarrhoea (TD1) and total number of warning signs at day two of illness without diarrhoea (T2), were not statistically significant in the omnibus test of model such as gender [$\chi^2(1) = 3.186, P = 0.074$], race/nationality [$\chi^2(21) = 26.437, P = 0.190$], T3 [$\chi^2(1) = 2.243, P = 0.134$], T4 [$\chi^2(1) = 1.864, P = 0.172$], T5 [$\chi^2(1) = 1.618, P = 0.203$], TD2 [$\chi^2(1) = 3.070$,

$P = 0.080$], TD3 [$\chi^2(1) = 1.940, P = 0.164$], TD4 [$\chi^2(1) = 1.346, P = 0.246$] and TD5 [$\chi^2(1) = 2.288, P = 0.130$]. Table 2 displays the univariate logistic regression of statistically significant omnibus test between the predictor variables and outcome variable.

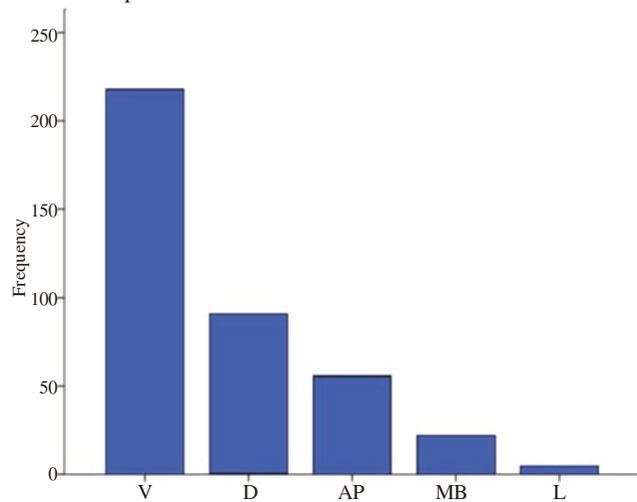


Figure 1. Frequency of the warning signs at Day 1 of illness. V: Vomiting; D: Diarrhoea; AP: Abdominal pain; MB: Mucosal bleed; L: Lethargy.

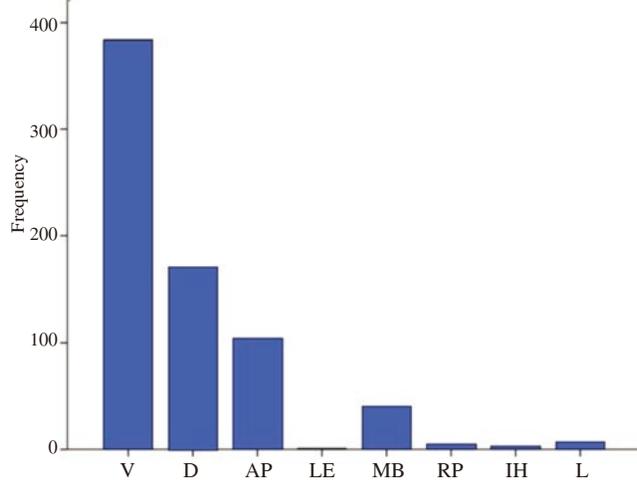


Figure 2. Frequency of the warning signs at Day 2 of illness. V: Vomiting; D: Diarrhoea; AP: Abdominal pain; LE: Liver enlargement; MB: Mucosal bleed; RP: Reduced platelet; IH: Increased haematocrit; L: Lethargy.

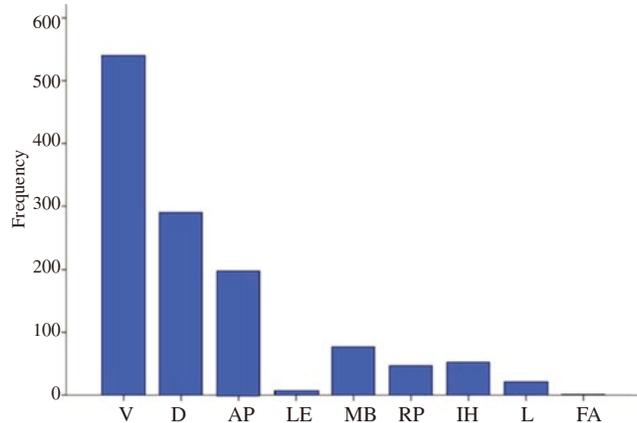


Figure 3. Frequency of the warning signs at Day 3 of illness. V: Vomiting; D: Diarrhoea; AP: Abdominal pain; LE: Liver enlargement; MB: Mucosal bleed; RP: Reduced platelet; IH: Increased haematocrit; L: Lethargy; FA: Fluid accumulation.

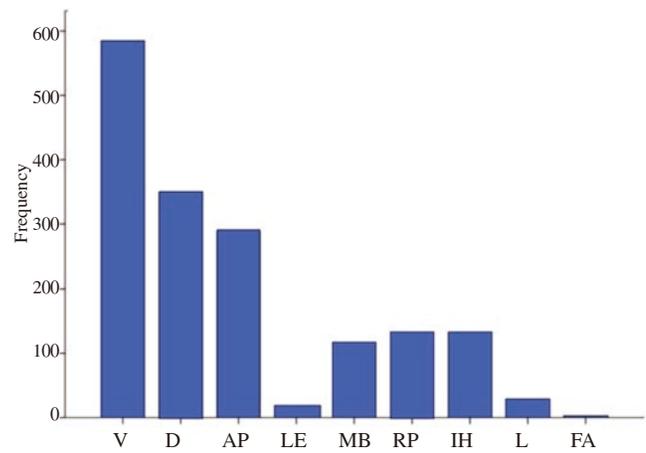


Figure 4. Frequency of the warning signs at Day 4 of illness. V: Vomiting; D: Diarrhoea; AP: Abdominal pain; LE: Liver enlargement; MB: Mucosal bleed; RP: Reduced platelet; IH: Increased haematocrit; L: Lethargy; FA: Fluid accumulation.

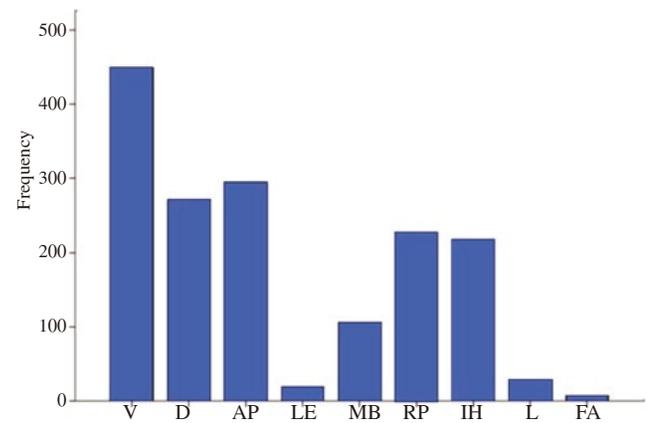


Figure 5. Frequency of the warning signs at Day 5 of illness. V: Vomiting; D: Diarrhoea; AP: Abdominal pain; LE: Liver enlargement; MB: Mucosal bleed; RP: Reduced platelet; IH: Increased haematocrit; L: Lethargy; FA: Fluid accumulation.

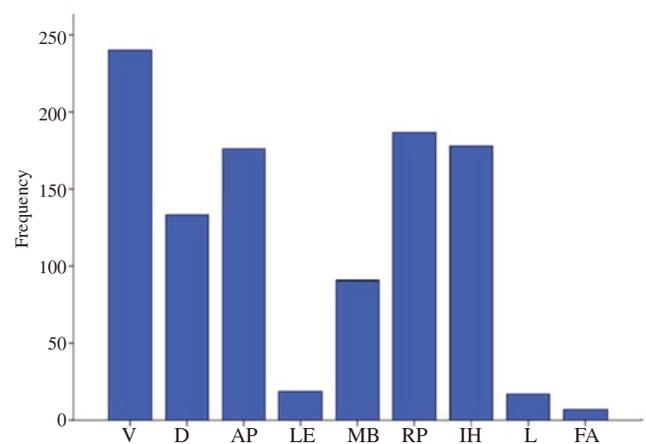


Figure 6. Frequency of the warning signs at Day 6 of illness. V: Vomiting; D: Diarrhoea; AP: Abdominal pain; LE: Liver enlargement; MB: Mucosal bleed; RP: Reduced platelet; IH: Increased haematocrit; L: Lethargy; FA: Fluid accumulation.

In the multivariate analysis using forward LR method, variable in the equation of the final model was only age for T3, T4, T5, TD2, TD3, TD4 and TD5. Thus only T1, T2 and TD1 were compared when lethargy was removed from the models. Table 3 presented the multivariate logistic regression between the predictor variables and outcome variable for T1, T2 and TD1 with and without lethargy being removed. Model T1 and T2 were the best fit model for ROC and it was presented in Table 4.

Table 2

Univariate logistic regression of statistically significant omnibus test between the predictor variables and outcome variable.

Predictor variable	Beta (B)	OR (95% CI)
Age	-0.019 ^b	0.981 (0.967–0.995)
T1	0.573 ^c	1.774 (1.319–2.387)
T2	0.276 ^a	1.318 (1.025–1.694)
TD1	0.454 ^c	1.575 (1.242–1.998)

OR: Odds ratio; CI: Confidence interval. ^a: P-value < 0.05; ^b: P-value < 0.01; ^c: P-value < 0.001.

Table 3

Multivariate logistic regression between the predictor variables and outcome variable for T1, T2 and TD1 with and without lethargy being removed.*

Model	Beta (B)	OR (95% CI)	Nagelkerke R ²
Model T1			0.016
Step 1			
Constant	-2.319	-	
T1	0.573 ^c	1.774 (1.319-2.387)	
Step 2			0.024
Constant	-1.843	-	
T1	0.551 ^c	1.735 (1.287-2.340)	
Age	-0.018 ^a	0.982 (0.969-0.996)	
Model T1 (lethargy removed)			0.015
Step 1			
Constant	-2.318	-	
T1	0.576 ^c	1.780 (1.315-2.408)	
Step 2			0.023
Constant	-1.841	-	
T1	0.552 ^c	1.737 (1.282-2.355)	
Age	-0.018 ^a	0.982 (0.969-0.996)	
Model T2			0.009
Step 1			
Constant	-1.678	-	
Age	-0.019 ^b	0.981 (0.967-0.995)	
Step 2			0.014
Constant	-1.789	-	
Age	-0.019 ^b	0.982 (0.968-0.995)	
T1	0.261 ^a	1.298 (1.008-1.671)	
Model TD1			0.015
Step 1			
Constant	-2.322	-	
TD1	0.454 ^c	1.575 (1.242-1.998)	
Step 2			0.023
Constant	-1.839	-	
TD1	0.439 ^c	1.551 (1.222-1.970)	
Age	-0.018 ^a	0.982 (0.969-0.996)	
Model TD1 (lethargy removed)			0.015
Step 1			
Constant	-2.320	-	
TD1	0.453 ^c	1.573 (1.237-2.000)	
Step 2			0.023
Constant	-1.836	-	
TD1	0.437 ^c	1.548 (1.216-1.971)	
Age	-0.018 ^a	0.982 (0.969-0.996)	

OR: Odds ratio; CI: Confidence interval. *The forward LR of model T2 did not include total number of warning signs at day 2 of illness when lethargy was removed, thus not presented in the table. ^a: P-value < 0.05; ^b: P-value < 0.01; ^c: P-value < 0.001.

Table 4

Receiver operating characteristics (ROC) of model T1 and T2.

Model	P cut-offs	PPV	NPV	SENS	SPEC	AUC (SE of AUC)	P-value
T1	0.0506	10.1%	96.4%*	99.4%	1.8%	0.604 (0.023)	< 0.001
	0.2149	22.7%*	90.1%	2.9%	98.9%		
T2	0.0503	10.2%	96.4%*	99.4%	1.8%	0.599 (0.024)	< 0.001
	0.1658	23.8%*	90.1%	2.9%	99.0%		

PPV: Positive predictive value; NPV: Negative predictive value; SENS: Sensitivity; SPEC: Specificity; AUC: Area under the curve; SE: Standard error. *: Highest PPV and NPV of that model with its corresponding SENS and SPEC.

4. Discussion

The results of this study indicated that the best fit predictive models were T1 and T2. This was derived from the analysis that was performed on the 1700 recruited patients where it predominantly comprised of males and adults. An analysis of results between the predictor variable and outcome variable by using both univariate and multivariate analysis led to statistically significant results for the age variable, T1, T2 and TD1. T1 and T2 models were chosen instead of TD1 and models without lethargy for they had similar Nagelkerke R square and were consistent with the warning signs in the WHO guidelines.

Similar study has developed statistical model for prediction by using the various variables of warning signs along with fever duration and fever on admission. Unfortunately, the fever duration variable requires the disease to progress for few days in order to correctly estimate the prediction. Shorter of the fever duration is likely to develop severe dengue, thus using this model will impose a risk where clinicians might choose to wait longer before admitting the patient for close monitoring and treatment[10]. In this proposed model of T1 and T2 for predicting severe dengue, clinician may use it on the first day or second day to triage the patient for admission or to follow-up the patient vigilantly if they are tested positive in the models (above the proposed P cut-offs). Ideally, prediction should be done before the critical phase when complication develops[3,11-17].

Our cohort of patients were generally younger compared to some studies[9,10,18,19], but similar to other studies[20,21]. However, our study cohort agreed that the amount of adult male was higher compared to children and female[20,22,23]. The warning signs frequency were generally agreeable to the existing literature where vomiting and diarrhoea were the predominant symptoms[24,25]. However, Thein *et al.* found that abdominal pain or tenderness was the predominant symptoms[18]. It is worth noting that diarrhoea was not part of the warning signs and was deemed as uncommon[5,26]. Interestingly, the frequency of having diarrhoea was higher compared to other warning signs, with the exception of vomiting. Hence, clinician could possibly miss severe dengue cases whereby diarrhoea is the only presenting symptom or misdiagnose dengue with warning signs with a non-dengue illness such as acute gastroenteritis. In these situations, it is a dilemma for the clinician in triaging the patients. Diarrhoea could be a new emerging symptom and it is possible that there will be a shift of the original predominant symptoms in the future. A re-look into the international guidelines on the warning signs may be beneficial so that dengue cases will not be missed. Thus far, the pathogenesis of the disease was unable to provide sufficient explanation as to why diarrhoea occurs.

The model developed, though statistically significant in predicting the disease, was unable to achieve optimum PPV and NPV. SENS and SPEC were not used for the selection of the cut-offs because PPV and NPV will be more helpful in decision-making for the clinicians. In view of the severity of the disease, it is ideal to have higher PPV compared to NPV. Unfortunately, the PPV for all the cut-offs for both models T1 and T2 was only less than 24%. This will in turn increase the burden of the hospital by wrongly admitting the patient when they would not develop severe dengue. Hence, NPV is rather valuable which will allow a better decision making where patients can be safely managed as outpatient if they are tested negative for the models. Based on the same cohort with P < 0.506 (model T1) and P < 0.503 (model T2) cut-offs, only one patient with severe dengue will be wrongly tested negative (false negative) using the models. However, only 27 (1.6%) patients of this cohort can be safely managed as outpatient. Therefore, it is still an unsatisfactory model to triage the patients effectively in order to reduce the healthcare burden.

Other limitations can affect the models' predictability: (i) The

models were based on cases that were confirmed by laboratory results. Due to epidemics, there were times when the test ran out of stock while at other times, the test was performed too early during the infection period when it was unlikely to detect the antibodies. This will in turn underreport the true incidence of the disease. (ii) Some of the dengue IgM tests were denoted as 'equivocal' and a repeat test was required. Unfortunately, there were no repeats of the test for some cases. (iii) Due to the lack of specificity of each warning sign such as persistent vomiting and lethargy, the model was subjected to selection bias whereby clinicians might misdiagnose based on their own clinical judgement. (iv) Some of the cases were excluded from this study due to the lack of rise in both HCT and a concurrent reduction in platelet. Therefore, although cases were laboratory diagnosed positive, the cases were not deemed as dengue with warning sign with only either a platelet reduction or a rise in HCT. (v) The models must be accompanied by a diagnostic test for dengue such as NS1 Ag rapid test kit to differentiate other non-dengue illnesses. (vi) Pregnancy status was not included into the multivariate logistic regression analysis due to low sample size. Pregnancy with dengue infection should be investigated separately because they could develop more serious complication than other individuals.

In conclusion, the models developed in this study might not reduce the burden effectively. Clinicians may use the models to predict the outcome and triage the dengue infected patients with minimal effect on to the overall burden of the disease. However, the models must be re-validated in their own clinical settings or population as the NPV and PPV might vary which may alter the effect size. Furthermore, the risk and benefit in selecting the different cut-off values should be evaluated before implementing such models.

Conflict of interest statement

We declare that we have no conflict of interest.

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