



Original article

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The accuracy of newly proposed warning signs in the third edition of Malaysian guideline on the management of dengue infection in adult

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ABSTRACT

Objective: To evaluate the accuracy of persistent vomiting and persistent diarrhoea proposed in the Malaysian dengue guideline.

Methods: The eligibility criteria were dengue patients with vomiting or/and diarrhoea at the earliest day of illness without other warning signs. Vomiting and diarrhoea categorised by three or more episodes over 24 h were considered as warning signs. Sensitivity, specificity, positive predictive value and negative predictive value were calculated.

Results: There were a total of 479 patients, of whom 36 (7.5%) got severe dengue and 443 (92.5%) got dengue with warning signs. The overall accuracy ranged from 33.3% to 72.7% for sensitivity, 28.8% to 56.5% for specificity, 1.8% to 14.5% for positive predictive value and 88.5% to 96.3% for negative predictive value. There were 16 false negative.

Conclusions: The newly proposed warning signs in the third edition of Malaysian dengue guideline may not be effective in predicting severe dengue.

1. Introduction

The global burden of dengue is estimated to be 390 million infections per year[1]. The health care burden increases when patients infected dengue further developed complications leading to severe dengue. Hence, warning signs were used to predict the progression and severity of the disease[2].

The World Health Organization (WHO) 2009 guidelines on dengue have been developed for clinical practice all over the world including Malaysia[2]. Its clinical classification has been adopted. But recently, the new third edition of Malaysian dengue clinical practice guideline has been developed with the addition of persistent diarrhoea as warning sign to the existing WHO 2009 classification. Furthermore, persistent vomiting and persistent diarrhoea for three or more times over 24 h were considered as warning signs[3].

It is essential to evaluate and validate these two modified warning signs to the international guidelines in the Malaysian population.

The accuracy of these modified warning signs is important in order to correctly classify the clinical spectrum of dengue infection. More importantly, it will assist clinicians to accurately predict the outcome of dengue infection for timely treatment. Hence, admission to the hospital is warranted, if any one of the warning signs is present. This study aimed to evaluate the accuracy of persistent vomiting and persistent diarrhoea proposed in the third edition of Malaysian clinical practice guideline on the management of dengue infection in adult.

2. Materials and methods

2.1. Study design

A subset of a previously collected data was used in this study based on the pre-specified eligibility criteria[4]. Briefly, the subset of data was obtained from January to September 2014 in a retrospective cohort study with all patients being either dengue immunoglobulin M or nonstructural 1 antigen positive, or both dengue immunoglobulin M and nonstructural 1 antigen positive, with clinical diagnosis of dengue with warning signs or severe dengue based on WHO 2009. Patient with malignancies especially blood cancers such as leukemia were excluded to avoid

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misclassification of clinical diagnosis.

The eligibility criteria in this study were patients presenting with vomiting or/and diarrhoea at the earliest day of illness without any other warning signs. If other warning signs presented along with vomiting and diarrhoea, the patient will be admitted to the hospital for treatment anyway. Thus, presence of vomiting and diarrhoea with frequency of three or more times in a day along with other warning signs did not alter the decision to admit the patient to the hospital.

2.2. Statistical analysis

A descriptive analysis was performed for gender, race, age, final diagnosis based on WHO 2009, In addition, the number of patients when the earliest symptom appeared and when severe dengue diagnosis made was described. The frequency of vomiting and diarrhoea was categorised according to the third edition of Malaysian clinical practice guideline on the management of dengue infection in adult, that was vomiting or diarrhoea of three or more episodes over 24 h were considered as warning signs[3]. Hence, patients presenting both vomiting and diarrhoea were considered as warning signs, if anyone of the two symptoms had three or more episodes over 24 h.

With the WHO 2009 as a reference standard, the analyses of sensitivity (SENS), specificity (SPEC), positive predictive value (PPV), and negative predictive value (NPV) were performed for three different groups: patient with both vomiting and diarrhoea, vomiting alone and diarrhoea alone. Missing data was dealt with “worst-and-best-case scenario” analysis. The “worst-case” was defined as having warning signs and “best-case” was defined as without having warning signs.

Definition for terms used was made. True positive was defined as that patients with severe dengue were correctly identified; false negative was defined as that patients with severe dengue were wrongly identified; false positive was defined as that patients with warning signs were wrongly identified; and true negative was defined as that patients with warning signs were correctly identified. The important aspect of clinical management was to prevent dengue mortality. Hence, all of the false negative cases of the three groups were traced to identify warning signs other than vomiting and diarrhoea that could have warranted admission, even if the frequency of vomiting and diarrhoea did not reach three or more times a day. All analyses were performed using Microsoft Excel 2016.

3. Results

A total of 479 patients fulfilling the eligibility criteria were identified from a cohort of 1700 patients. Among the 479 patients, 300 were male (62.6%) and 179 were female (37.4%). About 72.7% of the total patients were Malaysian with 261 Malay (75.0%), 66 Chinese (19.0%), 18 Indian (5.2%) and three other Malaysian not classified (0.9%). The mean age was 27.3 years old with standard deviation of 11.3 years. Among all the diagnosed patients by WHO 2009, 36 patients were severe dengue (7.5%) and 443 patients were dengue with warning signs (92.5%). The number of patients in each category was 91 (19.0%) with vomiting and diarrhoea, 293 (61.2%) with vomiting alone and 95 (19.8%) with diarrhoea alone. Missing

data found in the frequency of vomiting and diarrhoea were 7.1%.

The majority of the patients presented their first symptom of illness during Day 1 (21.5%) and Day 4 (22.1%), followed by Day 2 (13.4%) and Day 3 (19.8%). Severe dengue diagnosis was mostly made during Day 5 (32.4%) and Day 6 (47.1%) (Table 1). Of the 34 severe dengue patients, eight (23.5%) had symptoms of vomiting and/or diarrhoea two or three days prior to the diagnosis. Six (17.6%) were four days prior to the diagnosis and only one (2.9%) patient had symptom on the day of severe dengue diagnosis (Table 2).

Table 1

The number of patients when the earliest symptom appeared and the diagnosis of severe dengue was made. *n* (%).

Days of illness	Number of patients with earliest symptom (<i>n</i> = 479)	Number of patients with severe dengue (<i>n</i> = 34 [*])
1	103 (21.5)	NA
2	64 (13.4)	NA
3	95 (19.8)	NA
4	106 (22.1)	NA
5	61 (12.7)	11 (32.4)
6	37 (7.7)	16 (47.1)
7	8 (1.7)	3 (8.8)
8	2 (0.4)	3 (8.8)
9	2 (0.4)	NA
10	NA	1 (2.9)
13	1 (0.2)	NA

NA: Not applicable; ^{*}: The total number of patients with severe dengue was 36 with two patients having missing data on the day of diagnosis.

Table 2

The number of patients with reference to the number of days when symptom first appeared before the diagnosis of severe dengue. *n* (%).

Number of days for symptom first appeared before the diagnosis of severe dengue	Number of patients (<i>n</i> = 34 [*])
0	1 (2.9)
1	4 (11.8)
2	8 (23.5)
3	8 (23.5)
4	6 (17.6)
5	4 (11.8)
6	2 (5.9)
9	1 (2.9)

^{*}: The total number of patients with severe dengue was 36 with two patients having missing data on the day of diagnosis.

The “worst-and-best-case scenario” analysis indicated a range of accuracy for the missing data with the highest difference of 18.2% SENS in the category of patients having vomiting alone. The overall accuracy for all categories was ranging from 33.3% to 72.7% for SENS, 28.8% to 56.5% for SPEC, 1.8% to 14.5% for PPV and 88.5% to 96.3% for NPV (Table 3). There were 16 false negatives with the assumption that the missing data were not considered as warning signs (frequency < 3/day). Among the 16 false negative patients, six (37.5%) patients did not have any other warning signs and seven (43.8%) patients had at least one warning signs other than vomiting and diarrhoea but occurred on the same day of the severe dengue diagnosis being made. Only three (18.8%) false negative patients had warning signs occurring one day prior to the severe dengue diagnosis.

Table 3

The analyses of SENS, SPEC, PPV and NPV for patients presenting with both vomiting and diarrhoea, vomiting alone and diarrhoea alone using the third edition of Malaysian dengue guideline.

Items	Number of patients (n)				Accuracy (%)			
	True positive	False negative	False positive	True negative	SENS	SPEC	PPV	NPV
Vomiting and diarrhoea	8	3	47, 57*	33, 23*	72.7	28.8–41.3	12.3–14.5	88.5–91.7
Vomiting alone	11, 15*	11, 7*	150, 177*	121, 94*	50.0–68.2	34.7–44.6	6.8–7.8	91.7–93.1
Diarrhoea alone	1	2	40, 54*	52, 38*	33.3	41.3–56.5	1.8–2.4	95.0–96.3

*: “Worst-and-best-case scenario” analysis for missing data, left datum for number of patients with no warning signs, right datum for number of patients with warning signs.

4. Discussion

Most patients presented with vomiting alone and most of them presented early during Day 1–Day 4. Diagnosis of severe dengue made most frequently on Day 6 and Day 7 represented the deterioration of the patients’ condition. Patients presented their symptoms mostly in two to four days earlier before severe dengue occurred. The accuracy of using persistent vomiting and persistent diarrhoea with frequency of three or more in 24 h as warning signs was variable. Results of PPV and NPV were as expected due to the low incidence of severe dengue among the dengue patients.

To our knowledge, no study has been conducted to assess the frequency of vomiting and diarrhoea in a patient. The results of warning signs evaluation using the third edition of Malaysian clinical practice guideline were not favourable due to its poor SENS. Poor SENS leading to high false negative rate has an implication on the mortality of dengue infected patients. The SENS analysed in this study cannot be explained by some potential flaws such as missing data and warning signs other than vomiting and diarrhoea which could have warranted admission even achieving less than three episodes of frequency of vomiting and diarrhoea. SENS analysis was performed for the missing data indicated that there was little effect which could bias the result. All false negative patients were traced back individually, but unfortunately, most of them were either not present with other warning signs or present with warning signs on the same day. Only three patients presented with warning signs one day before severe dengue, but it was a too short duration for early treatment. Thus, all 16 false negative patients with severe dengue could be missed with the newly proposed warning signs and this might affect the clinical outcome of dengue infection.

Comparing to the WHO 2009 guidelines on dengue management, the warning signs of persistent vomiting did not have specific criteria on the frequency[2]. Hence, the decision for it to be considered as warning signs can be variable. Though it could lead to varying clinical judgement, clinicians are more likely to consider any amount of vomiting to be warning signs. Furthermore, clinicians will also make the final decision based on other vital parameters assessed in the patient. Thus, WHO 2009 has high SENS with low false negative rate[5-7].

The third edition of Malaysian clinical practice guideline, however, provided a statement of intent that adherence to this guideline may not necessarily guarantee the best outcome in every case. Clinicians are to make decision based on the clinical presentation and resource setting[3].

The limitation of this study was that the population and presentation of symptoms might vary across the country and in other countries. This study uses data of all patients including children, but the

guideline is intended for adult. However, only 9.0% of patients were less than 15 years old. The data used were patients admitted to the hospital two years ago. It is unlikely that there will be any difference in the presentation of dengue infected patients in 2016 or the next subsequent years. Future prospective, nation-wide studies should be conducted to further evaluate and improve the guideline according to the best evidence available from time to time.

The newly proposed warning signs in the third edition of Malaysian clinical practice guideline on the management of dengue infection in adult, may not be effective in predicting severe dengue.

Conflict of interest statement

I declare that I have no conflict of interest.

Acknowledgments

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