Original Article

An evaluation of the World Health Organization's 1997 and 2009 dengue classifications in hospitalized dengue patients in Malaysia

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Abstract

Introduction: The latest revised version of the World Health Organization's dengue classification was released in 2009. A handful of studies have taken initiatives to evaluate the old and revised guidelines to determine early signs and symptoms of severe dengue. This retrospective study aimed to compare the classification of dengue using both the 1997 and 2009 guidelines in a selected cohort of dengue patients from Peninsular Malaysia between 2008 and 2012.

Methodology: Adult dengue patients were recruited from tertiary hospitals in two different states, Selangor and Kelantan, in Peninsular Malaysia. Their clinical manifestations were assessed.

Results: A total of 281 confirmed dengue patients were enrolled; the mean duration of illness at admission was five days. Of these, 88.6%, 10.7%, and 0.7% were classified according to the 1997 guidelines as having dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS), respectively. When the WHO 2009 guidelines were applied, 17.1%, 78.3%, and 4.6% were classified as dengue without warning signs, dengue with warning signs, and severe dengue, respectively.

Conclusions: Our data suggests that the revised WHO 2009 guidelines stratify a much larger proportion of patients into a category that requires a higher level of medical and nursing care.

Key words: dengue; WHO 1997; WHO 2009; Malaysia

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Introduction

Dengue is the most prevalent mosquito-borne viral disease affecting people in the tropic and sub-tropic regions of the world, caused by the infection of dengue virus (DENV). The virus exists as four related but antigenically distinct serotypes, namely DENV 1-4. These viruses are transmitted to humans via infected mosquitoes, namely *Aedes sp*. Individuals infected with any DENV serotype may remain asymptomatic or may present with symptoms ranging from mild febrile illness to severe and occasionally fatal hemorrhagic disease.

Globally, dengue fever and severe dengue cases have risen from less than 1,000 cases in 1955 to almost 1,000,000 cases in 2007. The number of countries reporting dengue cases has also increased to more than 60 countries [1]. Recently, Bhatt *et al*. [2] estimated an alarming 390 million dengue infection worldwide per year, which is three times higher than predicted by the World Health Organization (WHO). In Malaysia, the number of reported dengue cases has also shown an upward trend, with around 6,500 cases in 1995 to 32,767 cases in 2002 and more than 49,000

cases in 2007 [3]. All four DENV serotypes have been co-circulating in Malaysia [4].

Under the earlier WHO classification [5], patients infected with dengue were either classified as having dengue fever (DF) or dengue hemorrhagic fever (DHF) (Table 1). DHF patients were further stratified into four categories depending on severity, namely DHF-I, II, III, and IV. DHF-III and IV are defined as dengue shock syndrome (DSS) when patients manifest signs of circulatory failure. However, there were problems with this classification, as at times it proved difficult to apply in the clinical context. Furthermore,

Table 1. The old and new WHO dengue classifications (extracted from WHO 1997 and 2009)

WHO 1997 dengue classifications
Dengue Fever (DF) Acute febrile illness with two or more of the following: • Headache • Retro-orbital pain • Myalgia • Leukopenia • Anthralgia • Rash • Hemorrhagic manifestations • Supportive serology or occurrence at the same location as other confirmed cases of dengue fever
Dengue Hemorrhagic Fever (DHF) All of the following must be present: • Fever or history of acute fever, lasting 1-7 days, occasionally biphasic • Hemorrhagic manifestations: -Positive torniquet test; -Petechia, equimosis, purpura or bleeding from mucosa, gastrointestinal tract, injection sites or other locations; or -Haematemesis/melena • Thrombocytopenia (<100,000 platelets per mm^3) • Evidence of plasma leakage due to increased vascular permeability
Dengue Shock Syndrome (DSS) DHF with hypotension for age or narrow pulse pressure (< 20 mmHg), plus one of the following: • Rapid and weak pulse • Cold, clammy skin, restlessness
WHO 2009 dengue classifications
Dengue without warning signs Fever and two of the following: • Nausea, vomiting • Rash • Aches and pains • Leukopenia • Positive tourniquet test
Dengue with warning signs Dengue as defined above with any of the following: • Abdominal pain or tenderness • Persistent vomiting • Clinical fluid accumulation • Mucosal bleeding • Lethargy, restlessness • Liver enlargement > 2 cm • Laboratory: increase in HCT concurrent with rapid decrease in platelet count **Severe dengue** Dengue with at least one of the following criteria: • Severe plasma leakage leading to: -shock (DSS) -fluid accumulation with respiratory distress • Severe bleeding as evaluated by clinician • Severe organ involvement -liver: AST or ALT ≥ 1000 -CNS: impaired consciousness -failure of heart and other organ

there were patients with severe dengue manifestations that did not fulfil the criteria of DHF [6,7]. This was also seen in Malaysia [8,9]. Thus, this classification underwent a proposed revision by the WHO in 2009, when the DHF criteria was revised and replaced with dengue with or without warning signs and severe dengue (Table 1).

Several reports have evaluated the differences between the two classification schemes. A study conducted in 18 countries, of which Malaysia was one, showed that a higher percentage of dengue cases could not be classified when the WHO 1997 classification was applied, as compared to the revised classification [10]. Similarly, all the fatal cases during a five-year study in Singapore fulfilled the severe dengue criteria using the WHO 2009 classification, but only 36% fulfilled the same criteria using the WHO 1997 classification [11]. On the other hand, another study indicated that both definitions are sensitive, but the diagnosis of dengue becomes more challenging in elderly patients [12], suggesting that there are still limitations to both guidelines. Hence, a conclusion could not be drawn about its applicability.

Therefore, this study aimed to evaluate both classifications in identifying severe dengue cases in Malaysia.

Methodology

Ethics approval

The study was approved by the research and ethics committees of Universiti Sains Malaysia (USM) [(USMKK/PPP/JEPeM (211.3[6])], Universiti Teknologi MARA (UiTM) (600-RMI [5/1/6]), and the Malaysian Ministry of Health (MOH) (NMRR-09-1128-4211).

Sample collection

Four hundred and thirty-nine hospitalized suspected adult dengue patients, 13 years of age or older were recruited from three different hospitals, namely Hospital Universiti Sains Malaysia (HUSM), Hospital Raja Perempuan Zainab II (HKB), and Hospital Sungai Buloh (HSB). Among these, 185 confirmed dengue patients were from HUSM and HKB and were recruited between 2008 and 2010. Both hospitals are located in the state of Kelantan. Another 96 patients were confirmed dengue patients from HSB (recruited between 2010 and 2012), located in the state of Selangor. Blood samples were collected on the first day of admission, and the clinical data were retrieved from standardized case report forms after the patients were discharged. Laboratory confirmation, namely an IgM serological test, was carried out at the respective hospitals. These tests were independently repeated at least twice to confirm the results in addition to IgG serological tests. Dengue-specific IgG and IgM enzyme-linked immunosorbent assay (ELISA) kits (PanBio Diagnostics, Brisbane, Australia) were used in our laboratory. Diagnosis of dengue was determined by the expert clinicians at each study centre, respectively, based on the WHO criteria [1,5].

Inclusion and exclusion criteria

Informed consent was collected from all recruited patients upon hospitalization. Clinically diagnosed patients with positive serological test either for IgG, IgM, or both were included in this study. Patients who had been co-infected with other pathogens, or were negative for both IgG and IgM, were excluded.

WHO classifications [1,5]

Table 1 shows the previous and recent WHO classifications for dengue severity [1,5]. According to the Malaysian Ministry of Health [3], the increase of hematocrit (Hct) was defined as more than 46% and 40% for males and females, respectively. This is based on the local normal range of Hct in adults and is due to the unavailability of baseline Hct levels in the respective study centers.

Statistical analysis

Chi-square was used to evaluate statistical differences in categorical variables between groups. The Statistical Package for Social Sciences (SPSS) version 20 (SPSS Inc., Chicago, IL, USA) was used for data analyses.

Results

Among 439 patients, 281 (64%) dengue subjects were confirmed via serological tests (IgM and/or IgG). The excluded subjects were either negative for the serological tests, diagnosed to have co-infection during admission, or their clinical data were unavailable.

Table 2 shows the demographic data of the recruited subjects. Males comprised 60% of the subjects ($p = 0.001$), and more than 80% of the subjects were under 50 years of age. A summary of clinical data presentation with prevalence is shown in Table 3.

Table 2. Demographic data

		Number	%
Gender*	Male	168	59.79
	Female	113	40.21
Race	Malay	236	83.69
	Chinese	25	8.87
	Indian	11	3.90
	Other Malaysians	4	1.42
	Non-Malaysians	3	1.06
	N/A	2	0.71
Age group (years)	13-20	59	20.92
	21-30	85	30.14
	31-40	44	15.6
	41-50	47	16.67
	51-60	23	8.16
	61-70	14	4.96
	71-80	4	1.42
	>80	1	0.35
	Unrecorded	4	1.42

Data shows the distribution of gender, race, and age of subjects involved in this study (n=281). Other Malaysians: Siamese, Orang Asli and East Malaysians. Non-Malaysians: Bangladeshi, Indonesian and Pakistani. N/A: not available. *p = 0.001.

Table 3. Clinical data presentation with prevalence

		Number	%
Serology	IgM positive	249	88.61
	IgG positive	160	56.94
	IgM & IgG positive	128	45.55
Laboratory findings	Rise of hematocrit	176	62.63
	Thrombocytopenia	265	94.41
Clinical manifestations	Headache	172	61.20
	Chills	105	37.37
	Rash	74	26.33
	GI/abdominal pain	90	32.03
	Jaundice	5	1.78
	Muscle/joint pain	118	41.99
	Vomiting	142	49.82
	Diarrhea	92	32.74
	Purpura	2	0.71
	Petechiae	13	4.93
	Hepatomegaly	30	10.68
	Hepatosplenomegaly	1	0.36
	Spleenomegaly	1	0.36
	Pleural effusion/ascites	18	6.41
	Bleeding	64	22.78
Co-morbidity	DM	14	4.98
	Asthma	10	3.56
	HPT	6	2.14
	IHD	3	1.07
	Liver cirrhosis	3	1.07
	Others*	14	4.98

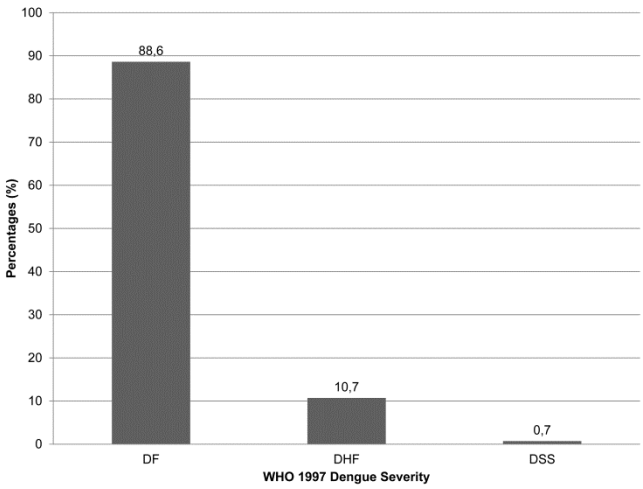
HPT: hypertension, DM: diabetes mellitus, IHD: ischemic heart disease
*Kidney failure, hepatitis, transaminitis, fatty liver, hyperlipidaemia, gastric and gout
Bleeding manifestations: epistaxis, haemoptysis, haematemesis, maleana, fresh rectal bleeding, haematuria, vaginal bleed, bleeding under the skin such as petechiae or purpura, or skin bruises and bleeding from the ear

When patients were classified according to the WHO 1997 guidelines, DF was found most frequently (88.6% of the cases), followed by DHF (10.7%) and DSS (0.7%) (Figure 1). The trend shifted when they were classified based on the WHO 2009 guidelines, whereby the majority of the patients were classified as dengue with warning signs (DW) (78.29%) (Figure 2).

In the 1997 classification, DSS was considered the severest form of dengue. Patients who were classified in this category expressed bleeding manifestations, thrombocytopenia, and pleural effusion and/or ascites. However, in the 2009 classification, only 67% of patients with severe dengue (SD) had bleeding manifestations, 95% had thrombocytopenia, and only 57 % had pleural effusion and /or ascites. Bleeding manifestations were included either by patients reporting or by detection of bleeding during their hospitalization. Pleural effusion and ascites were clinical findings made by the managing physician.

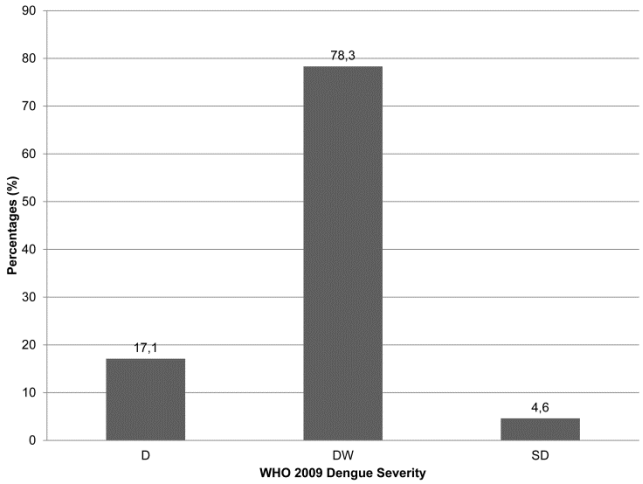
As shown in Table 4, 197 (70%) of the patients classified as DF by WHO 1997 were classified as DW, 48 (17%) as dengue without warning signs (D), and around 4 (1%) as SD when grouped by WHO 2009. Not all patients grouped under SD by WHO 2009 were classified as DSS by WHO 1997; in fact, about 1.6% of the DF patients (under WHO 1997 guidelines) were classified as SD. These were patients who had only hematemesis or increased AST as signs of severity and were not sufficient to be classified as DHF or DSS (Table 4).

Figure 1. Classification of study subjects according to WHO 1997 dengue guidelines.



DF: dengue fever, DHF: dengue hemorrhagic fever, DSS: dengue shock syndrome.

Figure 2. Classification of study subjects according to WHO 2009 dengue guidelines.



D: DF without warning signs, DW: dengue with warning signs, SD: severe dengue

Table 4. Concordance distribution of the study subjects according to WHO 2009 and WHO 1997 guidelines

		WHO 1997			Total (%)
		Dengue fever	Dengue hemorrhagic fever	Dengue shock syndrome	
WHO 2009	Dengue without warning signs	48	0	0	48 (17.1)
	Dengue with warning signs	197	23	0	220 (78.3)
	Severe dengue	4	7	2	13 (4.6)
	Total (%)	249 (88.6)	30 (10.7)	2 (0.7)	281 (100)

The percentage values in the total rows and columns are equivalent to Figures 1 and 2. Percentages are calculated based on the total number of patients.

Discussion

Several studies [10,13,14] reported that the revised WHO classification is more sensitive as well as more or comparably specific in identifying severe cases. In contrast, some still indicate that WHO 1997 is more sensitive – though less specific – in capturing severe cases [15].

We performed a retrospective observational study of dengue, which included 281 confirmed adult dengue patients (male: female ratio 1.5:1, range of age 13-88 years) admitted to the HUSM and HKB (between 2008 and 2010) as well as HSB (between 2010 and 2012).

We noted that the application of the two guidelines yielded different results. When classified according to WHO 1997 guidelines, our study cohort showed the highest percentage of DF, followed by DHF and DSS. This is in agreement with earlier reports [14,16,17]. However, the trend was different when the revised guidelines were used to classify the subjects. The highest percentage of cases were found to be DW, followed by D and SD. This finding was in line with that of Barniol *et al*. [10], whose study population included Malaysia. Although there are studies utilizing the 2009 guidelines [14,16], their findings are not similar to each other and are different from those of this study as well.

Our results show that DW was the most common classification (78.3%), followed by D (17.1%) and SD (4.6%). Narvaez *et al*. [14] found rates of both DW and SD to be similar and high in percentage (48% and 44%, respectively). Gan *et al*. [16] found D to be the most frequently occurring classification (48%), followed by DW (36%) and SD (16%). These differences could be due to a very large number of samples [16] and the use of a pediatric cohort [14].

In the current study, WHO 2009 captured higher cases of SD than those captured as DSS by WHO 1997. Some of these discrepancies were explained by patients who had increased AST or ALT > 1000U/L. This deranged liver function has also been seen during dengue infection in many populations [18-20]. However, these patients had been classified as DF or DHF under the 1997 guidelines.

The low percentage of DHF in comparison to DW is expected, as DHF requires the patients to meet all four criteria. DW has looser categories, which allows us to capture more patients potentially at risk of developing severe manifestations. This may eventually prompt clinicians to treat patients aggressively before they progress into SD. Our high percentage of hospitalized patients classified as DW is in line with the recommendation of the WHO 2009 guidelines that patients with warning signs are to be referred for in-patient management. However, this may increase the burden on the health care system.

Several limitations were encountered in this study. First, dengue infection was only confirmed by clinical diagnosis followed by dengue-specific IgG and IgM serological tests, as these are the routine practice in the hospitals where the sampling was done. However, these tests were independently repeated at least twice to confirm the results. Diagnosis based on a single laboratory confirmation through dengue-specific IgM serological tests have also been applied elsewhere [21,22]. Second, different clinicians may classify any clinical manifestations of dengue fever differently. Third, to avoid any potential sampling biases, we did a similar analysis separately on the two cohorts (the 2008-2010 cohort versus the 2010-2012 cohort) and found no significant different between them (data not shown). Therefore, we believe that the impact of such limitations is minimal.

Conclusions

To the best of our knowledge, we have provided a platform of pros and cons for both new and old dengue classifications with the data from a Malaysian cohort. The revised 2009 WHO classification stratifies a much larger proportion of patients into a category that requires a higher level of medical and nursing care. This would have a significant impact on hospital resources in the region and would require a heightened level of awareness among health care personnel about the dangers of dengue.

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