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ORIGINAL ARTICLE

Comparisons of dengue illness classified based on the 1997 and 2009 World Health Organization dengue classification schemes

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Background/Purpose: Dengue cases, traditionally classified as dengue fever (DF) or dengue hemorrhagic fever (DHF) by the World Health Organization (WHO) dengue classification 1997 scheme, are categorized into Group A (without warning signs), Group B [with warning signs (e.g., abdominal pain/vomiting/fluid accumulation/mucosal bleeding/lethargy/liver enlargement/increasing hematocrit with decreasing platelets)], or Group C (severe plasma leakage/severe bleeding/organ failure) by the WHO 2009 version. We compared differences in clinical/laboratory features between patients separately classified as DF/DHF and in Group A/B/C.

Methods: We performed a retrospective analysis of dengue patients diagnosed between 2008 and 2010.

Results: A total of 148 adult patients (119 DF/29 DHF; 64 Group A/77 Group B/7 Group C) were included. Compared with DF, significantly younger age, lower hospitalization rate, and higher platelet count were found in Group A. Compared with DHF, higher platelet count was found in Group B. Six of seven patients (86%) classified as Group C fulfilled the criteria of DHF. A cross tabulation showed DF cases were distributed in all of the severity groups stratified by the WHO dengue 2009 scheme (53.8% Group A/45.4% Group B/0.8% Group C); of the DHF cases, 23 (79%) were categorized as Group B, and six (20.7%) as Group C. All patients in Group A fell into the category DF.

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Conclusion: The WHO 2009 scheme is effective in identifying severe dengue cases. Heterogeneity in severity suggests careful severity discrimination in patients classified in Group B is needed. Our data suggest that it is safe to treat patients classified as Group A on an outpatient basis.

Introduction

Dengue is the most prevalent mosquito-borne viral infection and a major public health problem in the world, with approximately 2.5 billion people living in dengue endemic areas worldwide, and 50 million dengue infections occurring annually.[1–3] The conventional classification of dengue illness as dengue fever (DF) or dengue hemorrhagic fever (DHF) put forward by the World health organization (WHO) in 1975 was based on the results of studies in pediatric patients conducted at the Children's Hospital, Bangkok, Thailand.[4] The diagnosis of DHF established in dengue infection required the fulfillment of all of the following criteria: fever, hemorrhagia, thrombocytopenia ($<100 \times 10^9$ cells/L) and clinical evidence of plasma leakage resulting from increased vascular permeability.[5] The severity of DHF was categorized as follows: Grade I = fever accompanied by non-specific constitutional symptoms with the only hemorrhagic manifestation being a positive tourniquet test result; Grade II = spontaneous bleeding is observed, in addition to the manifestations of Grade I; Grade III = circulatory failure manifested by rapid and weak pulse and narrowing of pulse pressure or hypotension, with the presence of cold clammy skin; and Grade IV = profound shock with undetectable blood pressure and pulse. Grades III and IV were categorized as dengue shock syndrome (DSS).[5] Over the past decades, dengue has geographically expanded and increasingly affected adult populations.[1–3,6–10] A wide variety of dengue clinical manifestations have continuously been unveiled, adding to the major dengue presentations that were initially conceived to be mainly confined to fever and hemorrhagia.[11–13] Of note, It has been increasingly reported that severe dengue might not fulfill the criteria of DHF/DSS, yet put affected patients at high risk for mortality.[14–19] Numerous reports on critically ill dengue affected patients who died of causes other than DHF/DSS have urged for a revision of the convention WHO dengue classification, so that it could elicit practical warning signs in a timely fashion and provide appropriate treatment guidelines for severe dengue.[11–13,20–24] For practical reasons, the latest WHO dengue classification scheme issued in 2009 stratified dengue-affected patients, based on the clinical manifestations, laboratory parameters and the clinical-service delivery, into severe dengue and non-severe dengue cases.[1] However, the usefulness of WHO dengue classification 2009 scheme has not yet been fully evaluated.[1] Taiwanese clinicians are particularly inexperienced with the WHO 2009 dengue classification and treatment guidelines as most of the large dengue epidemics in Taiwan occurred before 2009.[24,25] The aim of this study was to evaluate the difference in clinical and laboratory features between patients who were separately classified based on the WHO classification 1997 and 2009 schemes, and the implications of these differences will be discussed.

Materials and methods

Patients and definitions

Patients with a diagnosis of acute dengue virus (DENV) infection admitted to Kaohsiung Chang Gung Memorial Hospital (KSCGMH), a 2700-bed medical facility serving as a primary and tertiary referral center in southern Taiwan, between 2008 and 2010 were included for retrospective analysis. The medical charts of the included patients were reviewed for retrieval of demographic, clinical, laboratory and imaging information. All included dengue cases were confirmed by at least one of the following criteria: (i) a positive reverse transcriptase-polymerase chain reaction (RT-PCR) result in acute-phase serum, (ii) a positive result for specific immunoglobulin M antibody in acute-phase serum, (iii) a fourfold increase in dengue-specific hemagglutination inhibition titer in convalescent serum as compared with that in acute–phase, and (iv) a dengue-specific nonstructural glycoprotein NS1 detected in acute-phase serum.[26–28] These diagnostic tests were performed by the Taiwan Center for Disease Control (CDC, Taiwan).

All included patients had their blood sampled for the assay of hemogram upon their arrival at KSCGMH. Additional blood chemistry and follow-up hemogram tests during hospital stay were carried out at the discretion of his or her physician as was clinically indicated. An organ impairment in the dengue-affected patient referred to any of the following clinical conditions: pulmonary edema, respiratory failure, severe gastrointestinal tract bleeding, severe hepatitis and rhabdomyolysis.[1] Severe hepatitis was defined as an elevated alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >1000 U/L [normal range (NR), ALT and AST, <40 U/L],[1] rhabdomyolysis are five or more times the upper limit of normal serum creatine kinase (NR, 20–130 U/L) and/or presence of myoglobin in the blood and/or urine,[29] and severe gastrointestinal bleeding as the passage of large amount of tarry or bloody stool coupled with hemodynamic instability and/or rapid decrease in hemoglobin level.[13] Plasma leakage referred to the presence of pleural effusion, ascites, and/or

hemoconcentration. Hemoconcentration referred to >20% increase in hematocrit calculated as: (maximum hematocrit − minimum hematocrit) × 100%/minimum hematocrit.[1,5,13]

WHO dengue classification 1997 and 2009 schemes

The definitions and severity stratifications of dengue in the WHO 1997 and 2009 schemes are summarized in Table 1.[1,5] Briefly, the WHO 1997 scheme classified dengue disease into DF and DHF (Grades I–IV)[5]; the WHO 2009 scheme classified dengue disease into dengue without warning signs, dengue with warning signs (i.e., abdominal pain/tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleed, lethargy, liver enlargement >2 cm, and increase in hematocrit concurrent with rapid decrease in platelet count), and severe dengue.[1] Furthermore, the 2009 WHO scheme categorized dengue-affected patients into: (i) Group A = patients without warnings signs, (ii) Group B = patients with ≥ one warning sign, patients with ≥ one coexisting conditions (i.e., pregnancy, infancy, old age, obesity, diabetes mellitus, renal failure, and chronic hemolytic diseases), and/or those with certain social circumstances (e.g., living alone or living far from a healthcare facility), and (iii) Group C = patients with severe plasma leakage, severe bleeding, and/or organ impairment.[1]

Data collection and dengue classifications

The medical records of the included patients were reviewed. The demographics and evolutionary clinical, laboratory and imaging information of the included patients were retrieved and recorded in a case report form. These data were presented at a group discussion and the classified severity of dengue in individual patients based on WHO 1997 and 2009 classification schemes were the consensus of the participating infectious-disease physicians.

Statistical analyses

The included patients were separately classified as (i) DF or DHF, according to the 1997 WHO case classification, and (ii) Group A, Group B or Group C, based on the 2009 WHO case definitions. To evaluate the differences between the 2009 and 1997 WHO classification schemes, univariate analyses were performed to compare clinical, laboratory and imaging features of patients between (i) Group A and DF, (ii) Group B and DF, (iii) Group C and DF, (iv) Group A and DHF, (v) Group B and DHF, and (vi) Group C and DHF. A cross tabulation of Group A/B/C and DF/DHF was made. Student's *t* test or Mann-Whitney *U* test was used for comparisons between continuous variables, whereas the Chi-square test or Fisher exact test was used for comparison between dichotomous variables. A statistically significant difference was determined by a p value <0.05.

Ethics statement

The study was conducted with a waiver of patient consent approved by the Institutional Review Board of KSCGMH (Document No.: 100-3061B).

Results

Characteristics of the overall included patients

Of a total of 148 patients (83 men and 65 women; mean age, 45.2 ± 18.9 years) each involved in one dengue case included, 41 (27.7%) were diagnosed in 2008, 64 (43.2%) in 2009, and 43 (29.1%) in 2010. The demographic, clinical, laboratory and imaging information of the included patients is summarized in Tables 2 and 3. The mean interval from dengue onset to hospital presentation was 3.7 ± 1.9 days. The most common underlying condition was hypertension (20%) and diabetes mellitus (11.3%). The three leading symptoms were fever (85.8%), myalgia (64.9%) and rashes (60%). As for warning signs, nausea/vomiting was found in 43 (29.1%) patients, mucosal bleeding (gum bleeding, hematuria and/or gastrointestinal bleeding) in 33 (22.3%), abdominal pain in 32 (21.6%), and drowsiness in one (0.7%). Platelet transfusion was given to 40 (27%) patients. Hemoconcentration was noted in 16 (10.8%) patients. Pleural effusion was found in 16 (15.1%) of the 106 patients with chest X-ray available, and ascites was detected in seven (8%) of the 87 patients with abdominal sonography available. Of the overall 64 DENV serotypes identified, DENV-3 accounting for 53.1%, followed by DENV-2 (28.1%), DENV-1 (17.2%) and DENV-4 (1.6%). All of the included patients survived.

Description of the included patients classified by the WHO 1997 scheme (Tables 2 and 3)

Of the 148 included patients, 119 [80.4%; median age, 45.7 years (range, 7–75)] were classified as suffering DF, and 29 [19.6%; median age, 53.7 years (range, 11–83)] as DHF. Seventy two (60.5%) of DF patients were hospitalized. Among the 119 DF patients, hemorrhage (gum bleeding, gastrointestinal bleeding and/or hematuria) was found in 27 (22.7%), the median platelet count was 56.5×10^9 cells/L (range, 3.0–202 cells/L), the median peak hematocrit level was 42.8% (range, 31.5%–53.7%), platelet transfusion was given to 25 (21%) patients and rhabdomyolysis was found in one (0.8%).

Twenty seven (93.1%) of the 29 DHF (19 Grade I and 10 Grade II) patients were hospitalized. Among the 29 DHF patients, severe gastrointestinal bleeding and rhabdomyolysis each was found in two patients (each 6.9%), the median platelet count was 42.8×10^9 cells/L (range, 2.0–91), and the median peak hematocrit level was 44.7% (range, 27.7–58.2). and platelet transfusion was given to 15 (51.7%) patients. Fourteen DHF patients with RT-PCR data available, and DENV-3 was found to be the etiologic virus in seven (50%) of them.

Table 1 Severity stratifications of laboratory-confirmed dengue illness by the 1997 and 2009 World Health Organization (WHO) dengue classification schemes

1997 WHO classification schemes		2009 WHO classification schemes		
Dengue fever	Dengue hemorrhagic fever[a]	Dengue without warning signs[b] (Group A)	Dengue with warning signs[b] (Group B)	Severe dengue (Group C)
Acute illness with $\geq$ 2 of the following symptoms: • Fever • Headache • Retro-orbital pain • Myalgia • Arthralgia • Rash • Hemorrhagic manifestations	All the following: • Fever • Hemorrhagia (e.g., positive tourniquet test, petechiae, ecchymosis, purpura, and bleeding from mucosa, gastrointestinal tract, injection sites or other locations) • Thrombocytopenia (platelet count $<$100 000 cells/μL); • Evidence of plasma leakage due to increased vascular permeability (e.g., hemoconcentration, pleural effusion, ascites and/or hypo-proteinemia)	Patients who do not have warning signs[b] AND who are able: • to tolerate adequate volumes of oral fluid replacement • to pass urine at least once every 6 hours	Patients with any of following features: • Co-existing conditions such as pregnancy, infancy, old age, diabetes mellitus, and renal failure • Social circumstances such as living alone, living far from hospital • Existing warning sign[b]	Patients with any of the following features: • Severe plasma leakage with shock and/or fluid accumulation leading to respiratory distress • Severe bleeding • Severe organ impairment[c]

[a] Dengue hemorrhagic fever were categorized into grades I–IV (see text for details).

[b] Warning signs: abdominal pain or tenderness, persistent vomiting; clinical fluid accumulation, mucosal bleeding, lethargy, restlessness, liver enlargement $>$2 cm, increase in hematocrit concurrent with rapid decrease in platelet count.

[c] Severe organ impairment: severe hepatitis was defined as an elevated alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) $>$1000 U/L (normal range [NR], ALT and AST, $<$40 U/L),[1] rhabdomyolysis as $\geq$5 times the upper limit of normal serum creatine kinase (NR, 20–130 U/L) and/or presence of myoglobin in the blood and/or urine.[29]

Table 2 Demographic and clinical features of the included patients according to 1997 and 2009 World Health Organization (WHO) dengue schemes

Variable	Total cases ($N = 148$)	1997 WHO classification		2009 WHO classification			p (Gr A vs. DF)	p (Gr B vs. DF)	p (Gr C vs. DF)	p (Gr A vs. DHF)	p (Gr B vs. DHF)	p (Gr C vs. DHF)
		p (Gr C vs. DHF) ($n = 119$)	DHF ($n = 29$)	Group A ($n = 64$)	Group B ($n = 77$)	Group C ($n = 7$)						
Demographic and clinical features												
Age (yr)							0.007	0.004	NS	0.001	NS	NS
Mean	45.2 ± 18.9	43.8 ± 18.8	50.7 ± 19	36.1 ± 17.6	51.8 ± 16.8	55.4 ± 19.8						
Median (range)	48.3 (7–83)	45.7 (7–75)	53.7 (11–83)	34.5 (7–64)	56.2 (11–77)	60 (28–83)						
Male, *n* (%)	83 (56.1)	66 (55.5)	17 (58.6)	30(46.9)	48 (62.3)	5 (71.4)	NS	NS	NS	NS	NS	NS
Diabetes mellitus, *n* (%)	17 (11.5)	9 (7.9)	8 (27.6)	0 (0)	16 (20.8)	1 (14.3)	0.028	0.009	NS	<0.001	NS	NS
Hypertension, *n* (%)	30 (20.3)	18 (15.1)	12 (41.4)	4 (6.3)	22 (28.6)	4 (57.1)	NS	0.029	0.018	<0.001	NS	NS
Mean day presented to hospital after onset of symptoms	3.7 ± 1.9	3.7 ± 1.9	3.8 ± 1.9	3.8 ± 1.7	3.6 ± 1.9	4.4 ± 2.2	NS	NS	NS	NS	NS	NS
Hospital admission, *n* (%)	99 (66.9)	72 (60.5)	27 (93.1)	28 (43.7)	64 (83.1)	7 (100)	0.043	0.001	0.045	<0.001	NS	NS
Dengue fever with bleeding, *n* (%)	27 (18.2)	27 (22.7)	—	—	—	—	—	—	—	—	—	—
DHF grade I, *n* (%)	19 (12.8)	—	19 (65.5)	—	—	—	—	—	—	—	—	—
DHF grade II, *n* (%)	10 (6.8)	—	10 (34.5)	—	—	—	—	—	—	—	—	—
DENV-1, *n/N* (%)	11/64 (17.2)	9/50 (18)	2/14 (14.3)	2/23 (8.7)	9/37 (24.3)	0/4 (0)	NS	NS	NS	NS	NS	NS
DENV-2, *n/N* (%)	18/64 (28.1)	13/50 (26)	5/14 (35.7)	5/23 (21.7)	11/37 (29.7)	1/4 (25)	NS	NS	NS	NS	NS	NS
DENV-3, *n/N* (%)	34/64 (53.1)	27/50 (54)	7/14 (50)	16/23 (69.6)	16/37 (43.2)	3/4 (75)	NS	NS	NS	NS	NS	NS
DENV-4, *n/N* (%)	1/64 (1.6)	1/50 (2)	0/14 (0)	0/23 (0)	1/37 (2.7)	0/4 (0)	NS	NS	NS	—	NS	—
Platelet transfusion, *n* (%)	40 (27)	25 (21)	15 (51.7)	6 (9.4)	30 (39)	4 (57)	NS	0.009	0.049	<0.001	NS	NS
Pleural effusion, *n/N* (%)	16/106 (15.1)	0/78 (0)	16/28 (57.1)	0/33 (0)	12/66 (18.2)	4/7 (57.1)	—	<0.001	<0.001	<0.001	NS	NS
Ascites, *n/N* (%)	7/87 (8)	0/62 (0)	7/25 (28)	0/22 (0)	7/59 (11.9)	0/6 (0)	—	0.005	—	0.010	NS	NS
Gallbladder swelling, *n/N* (%)	14/87 (16.1)	9/62 (14.5)	5/25 (20)	2/22 (9.1)	10/59 (16.9)	2/6 (33.3)	NS	NS	NS	NS	NS	NS
Hepatomegaly, *n/N* (%)	2/87 (2.3)	0/62 (0)	2/25 (8.0)	0/22 (0)	2/59 (3.4)	0/6 (0)	—	NS	—	NS	NS	NS
Splenomegaly, *n/N* (%)	13/87 (14.9)	9/62 (14.5)	4/25 (16)	4/22 (18.2)	8/59 (13.6)	1/6 (16.7)	NS	NS	NS	NS	NS	NS
Severe hepatitis, *n* (%)	2 (1.4)	0	2 (6.9)	0	0	2 (28.6)	—	—	0.003	NS	NS	NS
Severe gastrointestinal bleeding, *n* (%)	2 (1.4)	0	2 (6.9)	0	0	2 (28.6)	—	—	0.003	NS	NS	NS
Rhabdomyolysis, *n* (%)	3 (2)	1 (0.8)	2 (6.9)	0	0	3 (42.8)	NS	NS	<0.001	NS	NS	0.040

(*continued on next page*)

Table 2 (*continued*)

Variable	Total cases ($N = 148$)	1997 WHO classification		2009 WHO classification			*p* (Gr A vs. DF)	*p* (Gr B vs. DF)	*p* (Gr C vs. DF)	*p* (Gr A vs. DHF)	*p* (Gr B vs. DHF)	*p* (Gr C vs. DHF)
		p (Gr C vs. DHF) ($n = 119$)	DHF ($n = 29$)	Group A ($n = 64$)	Group B ($n = 77$)	Group C ($n = 7$)						
Acute pulmonary edema, *n* (%)	1 (0.7)	0	1 (3.4)	0	0	1 (14.3)	—	—	NS	NS	NS	NS
Symptom/sign,[a] *n (%)*												
Fever	127 (85.8)	100 (84)	27 (93.1)	52 (81.3)	68(88.3)	7 (100)	NS	NS	NS	NS	NS	NS
Abdominal pain	32 (21.6)	22 (18.5)	10 (34.5)	0 (0)	31 (40.3)	1 (14.3)	<0.001	0.001	NS	NS	NS	NS
Retro-orbital pain	18 (12)	15 (12.6)	3 (10.3)	6 (9.3)	11 (14.3)	1 (14.3)	NS	NS	NS	NS	NS	NS
Bone pain	75 (50.7)	56 (49.6)	16 (55.2)	26 (40.6)	44 (57.1)	5 (71.4)	NS	NS	NS	NS	NS	NS
Myalgia	96 (64.9)	76 (63.9)	20 (69)	35 (54.7)	56 (72.7)	5 (71.4)	NS	NS	NS	NS	NS	NS
Cough	39 (26.4)	29 (24.4)	10 (34.5)	11 (17.2)	26 (33.8)	2 (28.6)	NS	NS	NS	NS	NS	NS
Headache	63 (42.6)	52 (43.7)	11 (37.9)	26 (40.6)	33 (42.9)	4 (57.1)	NS	NS	NS	NS	NS	NS
Rashes	88 (59.5)	71 (59.7)	17 (58.6)	37 (57.8)	47 (61)	4 (57.1)	NS	NS	NS	NS	NS	NS
Vomiting/nausea	43 (29.1)	32 (26.9)	11 (37.9)	12 (18.8)	27 (35.1)	4 (57.1)	NS	NS	NS	NS	NS	NS
Diarrhea	16 (10.8)	11 (9.2)	5 (17.2)	6 (9.4)	9 (11.7)	1 (14.3)	NS	NS	NS	NS	NS	NS
Drowsiness	1 (0.7)	0	1 (3.4)	0	0	1 (14.3)	—	—	NS	NS	NS	NS
Gum bleeding	13 (8.8)	10 (8.5)	3 (10.3)	0 (0)	12 (15.6)	1 (14.3)	0.016	NS	NS	0.028	NS	NS
Petechiae	61 (41.2)	46 (38.7)	15 (51.7)	24 (37.5)	33 (42.9)	4 (57.1)	NS	NS	NS	NS	NS	NS
Gastrointestinal bleeding	15 (10.1)	10 (8.5)	5(17.2)	0(0)	12 (15.6)	3 (42.9)	0.016	NS	0.024	0.002	NS	NS
Hematuria	7 (4.7)	6 (5)	1 (3.4)	0 (0)	6 (7.8)	1 (14.3)	NS	NS	NS	NS	NS	NS

DF = dengue fever; DHF = dengue hemorrhagic fever; Gr = Group; NS = not significant; n/N = no. of patients/no. of patients with data available.

[a] An individual patient might have more than one underlying disease/condition.

Table 3 Laboratory characteristics of the included patients according to 1997 and 2009 World Health Organization (WHO) dengue schemes

Variable	Total cases ($N = 148$)	1997 WHO classification		2009 WHO classification			p (Gr A vs. DF)	p (Gr B vs. DF)	p (Gr C vs. DF)	p (Gr A vs. DHF)	p (Gr B vs. DHF)	p (Gr C vs. DHF)
		DF ($n = 119$)	DHF ($n = 29$)	Group A ($n = 64$)	Group B ($n = 77$)	Group C ($n = 7$)						
Leukopenia (WBC $< 3.0 \times 10^9$ cells/L), n/N (%)	82/146 (56.2)	64/117 (54.7)	18/29 (62.1)	33/62 (53.2)	45/77 (58.4)	4/7 (57.1)	NS	NS	NS	NS	NS	NS
Leukocytosis (WBC $> 12.0 \times 10^9$ cells/L), n/N (%)	2/146 (1.4)	0/117 (0)	2/29 (6.9)	0/62 (0)	1/77 (1.3)	1/7 (14.3)	—	NS	NS	NS	NS	NS
Median platelet count (range) ($\times 10^9$ cells/L)	41 (2.0—202)	56.5 (3.0—202)	21 (2—91)	91.5 (3—202)	35 (2—186)	21 (6—38)	0.024	0.009	0.006	<0.001	0.006	NS
Median peak hematocrit (range) (%)	43.3 (27.7—58.2)	42.8 (34.5—53.7)	44.7 (27.7—58.2)	42.3 (35.4—53.4)	43.6 (34.5—58.2)	43.4 (27.7—53.7)	NS	NS	NS	0.013	NS	NS
ALT $>$ 40 U/L (normal value $<$ 40 U/L), n/N (%)	84/131 (64.1)	61/103 (59.2)	23/28 (82.1)	25/52 (48.1)	52/72 (72.2)	7/7 (100)	NS	NS	0.043	0.004	NS	NS
AST $>$ 40 U/L (normal value $<$ 40 U/L), n/N (%)	97/122 (79.5)	70/94 (74.5)	27/28 (96.4)	31/49 (63.3)	59/66 (89.4)	7/7 (100)	NS	0.025	NS	0.001	NS	NS
Hypoalbuminemia (<3.0 mg/dl) (normal range 4.5—3.0 mg/dl), n/N (%)	3/53 (5.7)	2/41 (4.9)	1/12 (8.3)	0/45 (0)	1/30 (3.3)	2/4 (50)	NS	NS	0.034	NS	NS	NS

ALT = serum alanine aminotransferase; AST = aspartate aminotransferase; DF = dengue fever; DHF = dengue hemorrhagic fever; Gr = group; NS = not significant; n/N = no. of patients/no. of patients with data available; WBC = white blood cell.

Description of the included patients classified by the WHO 2009 scheme (Tables 2 and 3)

Of 148 included patients, 64 [43.2%; median age, 34.5 years (range, 7—64)] were allocated to Group A, 77 [52%; median age, 56.2 years (range, 1—77)] to Group B, and seven [4.7%; median age, 60 years (range, 28—83)] to Group C.

Among the 64 patients [28 (43.7%) of the patients were hospitalized] in Group A, the three most common symptoms/sign were fever (81.3%), rashes (57.8%) and myalgia (54.7%), the median platelet count was 91.5×10^9 cells/L (range, 3 to 202), and the median peak hematocrit level was 42.3% (range, 35.4—53.4); platelet transfusion was given to six (9.4%) patients.

Among the 77 [64 (83.1%) of the patients were hospitalized] patients in Group B, the three leading symptoms were fever (88.3%), myalgia (72.7%) and bone pain (57.1%); gastrointestinal bleeding developed in 12 (15.6%), the median platelet count was 35×10^9 cells/L (range, 2—186), and the median peak hematocrit level was 43.6% (range, 34.5—58.2); platelet transfusion was given to 30 (39%) patients.

All the seven patients in Group C were admitted to hospital, and the three leading symptoms were fever (100%), bone pain, and myalgia (each 71.4%). The median platelet count was 21×10^9 cells/L (range, 6—38), and the median peak hematocrit level was 43.4% (range, 27.7—53.7); platelet transfusion was given to four (57%) patients. The detailed demographics, clinical and laboratory features of the patients in Group C are summarized in Table 4. Of the seven patients allocated in Group C, six (85.7%) patients were classified as suffering DHF Grade II (Patients 1, 2 and 4—7), and one as DF (Patient 3). Rhabdomyolysis was found in three patients (Patients 3, 6 and 7); severe hepatitis (Patients 1 and 6), severe gastrointestinal bleeding (Patients 2 and 6), and respiratory distress (Patients 4 and 5) each were found in two patients. Of the two patients experienced respiratory distress, pulmonary edema was noted in Patient 5, and persistent drowsiness with respiratory failure that necessitated mechanical ventilatory support was found in Patient 4. Ventilator associated pneumonia subsequently developed in Patient 4, and meropenem was thereby intravenously administrated. Of the three (Patients 3, 6, and 7) patients complicated with rhabdomyolysis, concurrent severe hepatitis and severe gastrointestinal bleeding were found in Patient 6. Of note, all of the three patients with rhabdomyolysis presenting with myalgia and weakness of both lower limbs. Tea-colored urine was overt in Patient 3; however, no evidence of plasma leakage was detected by chest radiography and frequent measurement of his hematocrit. DENV-3 was detected in three (75%) of the four patients in Group C with RT-PCR data available.

Table 4 Detailed demographic, clinical and laboratory information of the seven patients in Group C[a]

Patient no.	Age (yr)/ sex	Underlying condition(s)	DENV serotype	1997 WHO classification	Days from onset of symptoms to emergency department	Complication(s)
1	28/M	None	DENV-3	DHF grade I	7	Severe hepatitis
2	58/F	None	ND	DHF grade II	7	Severe GI bleeding (endoscopy revealed multiple gastric ulcers)
3	61/M	Hypertension	DENV-3	DF	3	Rhabdomyolysis
4	83/M	Hypertension; ischemic heart disease	ND	DHF grade II	5	Respiratory distress with endotracheal intubation; GI bleeding; ventilator associated pneumonia
5	61/F	Diabetes mellitus; hypertension	DENV-2	DHF grade II	3	Respiratory distress; pulmonary edema
6	31/M	None	DENV-3	DHF grade II	5	Rhabdomyolysis; severe hepatitis; severe GI bleeding
7	67/M	Hypertension	ND	DHF grade II	1	Rhabdomyolysis

DENV = dengue virus; DF = dengue fever; DHF = dengue hemorrhagic fever; F = female; GI = gastrointestinal; M = male; ND = no data; WHO = World Health Organization.
[a] All patients survived.

Clinical, laboratory and imaging features between dengue classified by WHO 2009 scheme and DF (Tables 2 and 3)

Group A vs. DF

Patients in Group A were significantly younger (36.1 ± 17.9 years vs. 43.8 ± 18.8 years; $p = 0.007$); had lower

Table 5 Cross tabulation showing ratios of dengue severity in patients (N = 148) separately classified based on the 1997 and the 2009 World Health Organization (WHO) dengue classification schemes

1997 WHO Classification	2009 WHO Classification			Subtotal
	Group A	Group B	Group C	
DF	64	54	1	119
W/X[a] (%)	64/119 (53.8)	54/119 (45.4)	1/119 (0.8)	
Y/Z[b] (%)	64/64 (100)	54/77 (70)	1/7 (14)	
DHF	0	23	6	29
W/X[a] (%)	0	23/29 (79.3)	6/29 (20.7)	
Y/Z[b] (%)	0	23/77 (30)	6/7 (86)	
Subtotal	64	77	7	Total = 148

Data are number of patients, unless otherwise indicated.
DF = dengue fever; DHF = dengue hemorrhagic fever.
[a] W/X = the patient number of Group A or B or C/the subtotal patient number of DF or DHF.
[b] Y/Z = the patient number of DF or DHF/the subtotal patient number of Group A or B or C.

prevalence of diabetes mellitus (0 vs. 7.9%; $p = 0.028$), lower frequencies of abdominal pain (0 vs.18.5 %; $p < 0.001$), gum bleeding (0 vs. 8.5%; $p = 0.015$), and gastrointestinal bleeding (0 vs. 8.4%; $p = 0.016$); lower hospital admission rate (43.7 vs. 60.2%; $p = 0.043$), and higher platelet count (median, 91.5 $\times$ 10^9 cells/L vs. 56.5 $\times$ 10^9 cells/L; $p = 0.024$).

Group B vs. DF
Patients in Group B were significantly older (51.8 $\pm$ 16.8 years vs. 43.8 $\pm$ 18.8 years; $p = 0$ .004); had higher prevalences of diabetes mellitus (20.8% vs. 7.9%; $p = 0.009$) and hypertension (28.6% vs. 15.1%; $p = 0.029$), higher incidences of pleural effusion (18.2% vs. 0; $p < 0.001$), ascites (11.9% vs. 0; $p =$ 0005), and abdominal pain (40.3% vs. 18.5%; $p = 0.001$); higher hospital admission rate (83.1% vs. 60.2%; $p = 0.001$), lower platelet count (median, 35 $\times$ 10^9 cells/L vs. 56.5 $\times$ 10^9 cells/L; $p = 0.009$), higher serum AST level (89.4% vs. 74.5%; $p = 0.025$), and higher proportion of receiving platelet transfusion (39% vs. 21%; $p = 0.009$).

Group C vs. DF
Patients in Group C were significantly had higher prevalence of hypertension (57.1% vs. 15.1%; $p = 0.018$), higher hospital admission rate (100% vs. 60.2%; $p = 0.045$), higher incidences of severe hepatitis (28.6% vs. 0; $p = 0.003$), rhabdomyolysis (42.8% vs. 0.8%; $p < 0.001$), gastrointestinal bleeding (42.9% vs. 8.4%; $p = 0.024$), severe gastrointestinal bleeding (28.6% vs. 0; $p = 0.003$), pleural effusion (57.1% vs. 0; $p < 0.001$); and hypoalbuminemia (50% vs. 4.9%; p = 0.034), lower platelet count (median, 21 $\times$ 10^9 cells/L vs. 56.2 $\times$ 10^9 cells/L; $p = 0.006$), higher serum ALT (100% vs. 59.2%; $p = 0.043$) levels, and higher proportion of receiving platelet transfusion (57% vs. 21%; $p = 0.049$).

Clinical, laboratory and imaging features between dengue classified by WHO 2009 scheme and DHF (Tables 2 and 3)

Group A vs. DHF
Patients in Group A were significantly younger (mean, 36.1 $\pm$ 17.6 years vs. 50.7 $\pm$ 19 years; $p =$ 0,001); had lower prevalences of diabetes mellitus (0 vs. 27.6%; $p < 0.001$) and hypertension (6.3% vs. 41.4%; $p < 0.001$); lower hospital admission rate (43.7 vs. 93.1%; $p < 0.001$), higher platelet count (91.5 $\times$ 10^9 cells/L vs. 21 $\times$ 10^9 cells/L; $p < 0.001$), lower peak hematocrit (median, 42.3% vs. 44.7%; $p = 0.013$), and lower incidences of gastrointestinal bleeding (0 vs. 17.2%; $p = 0.002$), gum bleeding (0 vs. 28%; $p = 0.010$), pleural effusion (0 vs. 57.1 %; $p < 0.001$) and ascites (0 vs. 28%; $p = 0.010$); lower proportion of receiving platelet transfusion (9.4% vs. 51.7%; $p < 0.001$).

Group B vs. DHF
Patients in Group B had significantly higher platelet count (median, 35 $\times$ 10^9 cells/L vs. 21 $\times$ 10^9 cells/L; $p = 0.006$).

Group C vs. DHF
Patients in Group C were had significantly higher incidence of rhabdomyolysis (42.8% vs. 6.9%; $p = 0.040$).

Cross tabulation of dengue Group A/B/C and DF/DHF (Table 5)

Cases of DF were distributed in all of the severity groups stratified based on the WHO dengue 2009 scheme; of the 119 DF cases, 64 (53.8%) were categorized as Group A, 54 (45.4%) as Group B, one (0.8%) as Group C. Cases of DHF were distributed in either Group B or Group C; of the 29 DHF cases, 23 (79.3%) were categorized as Group B, and six (20.7%) as Group C. Contrariwise, all of the 64 patients allocated in Group A were categorized as DF; 70% (54/77 patients) and 30% (23/77 patients) of Group B were categorized as DF and DHF, respectively; and 14% (1/7 patients) and 86% (6/7 patients) of Group C were categorized as DF and DHF, respectively.

Discussion

Clinical severity in dengue illness steps up from DF to DHF, as stratified based on the WHO dengue classification 1997 scheme,[5] and from Group A, Group B to Group C, as stratified based on its 2009 version.[1] Substantial significant differences in demographic, laboratory and clinical variables between Group A/B/C and DF/DHF shown in Results

suggest that stratifications based on the WHO dengue 2009 and 1997 schemes are not interchangeable in terms of evaluation of clinical severity of dengue illness. The advantages of applying the WHO dengue classification 2009 scheme are that what clinicians need at treating dengue are to keep vigilant eye on the emergence of clinically easily recognizable warning signs and severe dengue, and manage patients according to the established guidelines.[1] Our data show that if reclassified based on WHO dengue classification 2009 scheme, 53.8%, 45.4%, and 0.8% of DF cases fell into Group A, Group B, and Group C, respectively, while 79.3% and 20.7% DHF cases fell into Group B and Group C, respectively. These data suggest that only 53.8% of DF patients in the present series be considered appropriate for treatment on outpatient basis,[30] while another 46.2% of DF patients and all DHF patients probably or absolutely need hospitalization for strict observations and/or aggressive intervention.[1] Our data implicate the a great heterogeneity of DF in terms of clinical severity, and different levels of clinical severity of DF are discriminated by the WHO dengue classification 2009 scheme.

By contrast, 100% of the patients allocated in Group A in the current series were categorized as DF, and approximately 30% of Group B and 86% of Group C were categorized as DHF. These data suggest that when stratified by WHO dengue classification 2009 scheme, dengue patients classified in Group A should be treated on outpatient basis, and escalating proportions of dengue patients categorized from Group B to Group C need admission for close observation and/or intervention as necessary. Of note, the hospitalization rates in this series were found to be 60.5% in DF patients, 93.1% in DHF patients, and 43.7%, 83.1%, and 100% in patients in Group A, Group B, and Group C, respectively. In consistent with previous report, [31] our data suggest that the WHO 2009 scheme better discriminate different levels of clinical severity among dengue-affected patients.

In comparison to its 1997 version, the WHO dengue classification 2009 scheme were also reported to have a higher sensitivity and specificity in identifying dengue cases that clinically progress requiring intensive care.[31] As dengue features clinically dynamic change over time,[13,31] when being treated on outpatient basis for whatever reasons, the dengue-affected patient categorized in Group A or Group B and the family should be notified to pay careful attention to the potential emergence of any newly developing warning sign and/or exacerbation of the pre-existing warning sign(s) that necessitates hospitalization.

In addition to addressing what happens in dengue patients surrounding the plasma leakage and bleeding as the WHO 1997 version did, the WHO 2009 scheme include the warning signs as monitor targets and severe organ impairment as part of the criteria in severe dengue,[1] comprehensively depicting what happens in reality. For instance, clinical manifestations of dengue patients categorized in Group C in this series (Table 4) were obviously much better detailed by the WHO 2009 scheme than by its previous version. This is not surprising as the WHO 2009 version was written to provide practical guidance to deal with dengue, which often occurs as a large-scale epidemic in areas where medical resources are deficient. On top of that, the WHO 2009 scheme takes into account other factors such as coexisting conditions (e.g., pregnancy, infancy, old age, diabetes mellitus, and renal failure) and social circumstances (e.g., living alone and/or far from a hospital) when it comes to consideration for dengue patient hospitalization for close observation.[1]

During the 3-year-study period, there were more than 3000 cases of symptomatic dengue cases notified in Taiwan.[32] DENV-1 was circulating in 2008, while DENV-3 was the predominant serotype between 2009 and 2010 and DENV-2 was sporadically found in 2010.[32] DENV-2 was reported to be more clinically virulent and associated with severe manifestations in some series.[33,34] Of note, Narvaez et al.[31] reported that DENV-2 was significantly associated with DHF/DSS, suggesting that the WHO dengue 2009 scheme was no longer specific in identifying severe dengue due to DENV-2. The association of DENV-2 and clinical severity was not found in our series. Rather, DENV-3 was found to be the most common serotype detected in patients with DHF and in those categorized in Group C. The higher linking between DENV-3 and DHF/severe dengue in our series partly resulted from the fact that DENV-3 was the dominant serotype in circulation during the study period.

There are some limitations in our study. First, the study was conducted at a single medical center, and the dengue severity of patients may therefore be biased by referral pattern. Second, the small sub-grouped case numbers make the statistical power quite small. Third, being a retrospective study, missing data for some included patients were unavoidable.

In conclusion, data from this study show that the WHO 2009 scheme is effective in identifying severe dengue cases. Heterogeneity in severity suggested careful severity discrimination in patients classified in Group B by clinicians is needed. Our data suggests that it is safe to treat dengue-affected patients classified in Group A on outpatient basis.

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