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Original Article

Analyses of clinical and laboratory characteristics of dengue adults at their hospital presentations based on the World Health Organization clinical-phase framework: Emphasizing risk of severe dengue in the elderly

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Abstract *Background/Purpose:* Dengue clinically dynamically changes over time; the World Health Organization (WHO) dengue classification framework proposed 3 dengue clinical phases—febrile (days 1–3), critical (days 4–6) and recovery (days ≥7) phases. This study aimed to better understand clinical and laboratory characteristics in adults (≥18 years) suffering dengue in different clinical phases at their hospital presentations.
Methods: A retrospective analysis of adults suffering dengue between 2008 and 2014.
Results: Of the 669 included dengue adults, 146 (21.8%) were elderly (≥65 years), and 27 (4%) suffered severe dengue. When compared with those in febrile phase, significantly higher incidence of ascites, mucosal bleeding, and/or gastrointestinal bleeding; lower white blood cell (WBC) and platelet counts; higher hematocrit, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values were found in critical phase. When compared with their younger counterparts, elderly at febrile phase had significantly lower frequencies of bone pain, myalgia, headache and rash; higher frequencies of vomiting, pleural effusion and mucosal bleeding; higher WBC count, AST and ALT levels, and lower platelet count; in critical phase, elderly had significantly higher frequencies of pleural effusion, mucosal bleeding and gum

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bleeding. Four (0.6%) patients experienced severe dengue in recovery phase. Significantly higher proportions of elderly developed severe dengue in both febrile and critical phases as compared with younger adults.
Conclusions: Elderly had lower frequency of classical dengue symptoms, yet were at higher risk of development of severe dengue during their early dengue course. A small number of patients developed severe dengue at the WHO-proposed recovery phase.

Introduction

Dengue is one of the most important arthropod-borne viral diseases in humans.[1] The World Health Organization (WHO) estimated that 2.5 billion people living in tropical and subtropical areas are at risk for dengue and 50—100 million dengue cases develop annually.[1] Dengue classification schemes and treatment guidelines were issued by the WHO in 1997 and 2009.[1,2] The WHO 1997 version classified dengue diseases as dengue fever (DF), and dengue hemorrhagic fever (DHF)/dengue shock syndrome (DSS),[2] which subsequently proved to oversimplify the clinical manifestations of dengue, especially in adults. With a broad-spectrum of manifestations, dengue clinically ranged from constitutional symptoms with self-limiting fever to death with unpredictable clinical evolution and outcomes.[1—4] The WHO 2009 version categorized dengue into dengue (with or without warning signs) and severe dengue,[1] and to facilitate triage and management of dengue for frontline clinicians, proposed 3 dengue clinical phases based on the day(s) after the onset of dengue illness as follows: febrile (days 1—3), critical (days 4—6) and recovery (days ≥7) phases.[1,5] Of note, a prolonged febrile phase is followed by the recovery phase in some dengue patients, while the febrile and critical phases may overlap in some others.[1,2,6] During the febrile phase, up-surging fever, retro-orbital pain, headache, arthralgia, myalgia, malaise, nausea, and/or vomiting typically develop; mild hemorrhagic manifestations such as petechiae and mucosal bleeding may occur, and dehydration may emerge.[1—3] The pathophysiological hallmark in the critical phase of dengue is increased capillary permeability with extravasation of fluids.[7,8] During the critical phase, leukocytopenia, thrombocytopenia,[9] plasma leak that clinically manifested by hemoconcentration, pleural effusion and/or ascites are usually found-,[1—3] and severe bleeding and shock may develop.[1—3] Intensive monitor of the evolutionary clinical course and timely intravenous fluid resuscitation as necessary are the key to the successful treatment for dengue patients in question.[1,10] The critical phase usually lasts for 24—48 h, and the majority of dengue patients will then enter into the recovery phase,[1—3] in which re-absorption of the extravasated fluid into intravascular compartment occurs; pulmonary edema might develop if excessive intravenous fluids had been supplied.[1] Generally, dengue patients will improve during convalescence, despite that some patients may develop an itchy/non-itchy erythematous rash.[1,11] The aforementioned WHO-proposed dengue clinical phases and clinical manifestations typically occur in pediatric patients.[5,7—9] Of note, in adults suffering severe dengue, especially in those with comorbidity/comorbidities and/or being elderly, a great variety of additional clinical manifestations such as bacterial sepsis and multi-organ failure potentially develop throughout the dengue clinical course, especially at the patient's critical phase.[12—17] In Taiwan, dengue mainly affects adults, and a substantial number of patients were elderly with multiple comorbidities experienced dismal clinical outcomes.[18,19] As clinical manifestations of dengue result from the complex immunologic reactions between the host and the culprit dengue virus,[20—22] the clinical presentations in adults during the febrile, critical, or recovery phases might differ from those in pediatric dengue patients.[23] Better understanding and being alert to clinical problems arising during different WHO-framework dengue phases is very important in terms of rational approach when it comes to case management.

The aim of the present study was to evaluate adult patients' clinical and laboratory features found in the individual clinical phases (i.e., febrile, critical and recovery phases) proposed by the WHO dengue framework at their hospital presentations. The included dengue adults were further stratified by age for comparison of clinical and laboratory characteristics between elderly (≥65 years) and younger adults. This study may offer valuable information to clinicians in monitoring dengue adults and managing dengue cases in a timely manner.

Materials and methods

Ethics statement

The study was reviewed and approved by the Institutional Review Board of Chang Gung Memorial Hospital (201600196B0). Informed consent was not required as the data were analyzed anonymously.

Patients and setting

Clinical, laboratory and imaging information for adult patients (≥18 years) with laboratory-confirmed dengue virus (DENV) infection presented to Kaohsiung Chang Gung Memorial Hospital (a 2700-bed primary care and tertiary referral medical center in southern Taiwan) seeking

medical help during 2008–2014 were retrospectively analyzed. All dengue cases included in this study were serologically confirmed by at least one of the following test results: (i) positive DENV-specific real-time reverse transcription polymerase chain reaction (RT-PCR) (QuantiTect SYBR Green RT-PCR kit, Qiagen, Hilden, Germany),[24] (ii) a fourfold increase in DENV-specific immunoglobulin G antibody in the convalescence serum as compared with the acute-phase serum,[25] and (iii) detection of DENV-specific nonstructural glycoprotein-1 antigen (Bio-Rad Laboratories, Marnes-la-Coquette, France) in the acute-phase serum.[26,27] All diagnostic tests were performed by the Taiwan Center for Disease Control.[4]

Case classification and definitions

The dengue onset day (day 1) referred to the day in which symptoms suggestive of dengue (i.e., fever, retro-orbital pain, headache, arthralgia and/or myalgia) started developing; this day was identified based on the patient's description at history taking upon his or her hospital presentation. The dengue clinical phases were classified based on the WHO-proposed dengue scheme,[1] as follows: febrile (days 1–3 symptoms/signs onset), critical (days 4–6) and recovery ($\geq$7 days) phases. A patient might therefore be in any of these clinical phases at their hospital presentation seeking medical help.

Elderly patients referred to patients aged $\geq$65 years.[28,29] The included dengue cases were classified into dengue (with or without warning signs) and severe dengue based on the criteria recommended by the WHO 2009 dengue classification scheme.[1] Warning signs were those mentioned previously[1] with modifications, which included abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, and an increase in hematocrit/hemoglobin (>20%) with a concurrent rapid drop in platelet count within 24–36 h. Clinical fluid accumulation was defined as the new presence of pleural effusion and/or ascites which was disclosed by chest radiography and/or ultrasonography. Severe dengue was defined as the presence of the severe plasma leak leading to shock/respiratory distress, severe bleeding and/or severe organ impairment.[1] Severe plasma leak was defined as clinical fluid accumulation and/or hemoconcentration (an increase in hematocrit >20%), coupled with tachycardia (pulse >100/minute), hypotension (systolic blood pressure <90 mmHg) and/or a narrow pulse pressure (<20 mmHg).[1] Severe bleeding was defined as hematemesis, hematochezia or melena, coupled with hemodynamic instability (systolic blood pressure <90 mm Hg) and/or a rapid drop in hemoglobin (hemoglobin level <10 g/dL) within 48 h.[1] Severe organ impairment included altered consciousness, severe hepatitis (alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 1000 U/L) or myocarditis.[1]

Data extraction

A standardized form for data collection was designed. The data were retrieved from the hospital electronic medical records. Collected information included patients' demographics, symptoms/signs, laboratory data and radiographic imaging at patients' hospital presentations, and the time lapses from dengue onset to hospital presentation and to the development of severe dengue, as well as to fatality for deceased patients.

Statistical analysis

The included patients were separated into 3 groups according to the clinical phases (i.e., febrile, critical and recovery phases) at their hospital presentations, and to investigate the impact of age on the clinical and laboratory presentations, stratified analyses were performed for elderly vs. younger dengue adults within each group. Analysis of severe dengue cases vs. non-severe dengue cases was likewise performed. Clinical and laboratory variables between groups/stratified subgroups were compared with each another using univariate analysis. Categorical variables were compared using the Chi-square or Fisher exact tests, and continuous variables were compared using the Student's t or Mann–Whitney U test. A 2-tailed $p < 0.05$ was considered statistically significant.

Results

Patient characteristics

Among a total of 669 included dengue adults (mean age, 49.9 $\pm$ 16.7 years; 341 [51%] males and 146 [21.8%] elderly), non-severe dengue with and without warning sign(s) were found in 320 (47.8%) and 322 (48.1%) patients, respectively, while 27 (4%) patients developed severe dengue; fatality resulting from refractory shock was found in 2 (0.3%) patients. Major underlying diseases found in these patients included hypertension (24.7%), diabetes mellitus (type 2 diabetes mellitus hereof) (14.2%), neoplasm (3.6%) and chronic kidney disease (2.6%). Among the overall included dengue patients, 338 (50.5%) (mean age, 50.7 $\pm$ 17.0 years; 85 [25.2%] elderly) presented to hospital in their febrile phase, 253 (37.8%) (mean age, 48.0 $\pm$ 16.8 years; 46 [18.2%] elderly) in critical phase, and 78 (11.6%) (mean age, 47.9 $\pm$ 15.7 years; 15 [19.2%] elderly) in recovery phase. The 3 leading symptoms found in different clinical phases were: fever (94.9%), myalgia (58.9%) and headache (42%) in febrile phase; fever (92.1%), myalgia (52.6%) and rash (47%) in critical phase, and rash (68%), fever (52.6%) and myalgia (48.7%) in recovery phase.

As for the 146 elderly dengue patients, 85 (58.3%) were admitted in their febrile phase, 46 (31.5%) in critical phase, and 15 (10.3%) in recovery phase. The leading symptoms/signs, in decreasing order, were fever (94%), myalgia (48.2%) and persistent vomiting (34.1%) for febrile phase; fever (95.7%), myalgia (52.2%) and bone pain (41.3%) for critical phase; and rashes and abdomen pain (each 46.7%) as well as fever and headache (each 33.3%) for recovery phase. Clinical and laboratory characteristics of the included patients in different dengue clinical phases, and differences between elderly and younger adult patients are shown in Table 1.

Table 1 Comparisons of the clinical and laboratory characteristics between elderly (≥65 years; N = 146) and younger (18–64 years; N = 523) dengue adults in the WHO-proposed febrile (days 1–3), critical (days 4–6), and recovery (days ≥ 7) phases[a] at their hospital presentations.

Variable	Febrile phase			*P* (A vs. B)	Critical phase			*P* (C vs. D)	Recovery phase			*P* (E vs. F)
	Total (N = 338)	Elderly (N = 85) (A)	Non-elderly (N = 253) (B)		Total (N = 253)	Elderly (N = 46) (C)	Non-elderly (N = 207) (D)		Total (N = 78)	Elderly (N = 15) (E)	Non-elderly (N = 63) (F)	
Symptom/sign[b], no. (%)												
Fever	319 (94.9)	80 (94)	239 (94.5)	>0.99	233 (92.1)	44 (95.7)	189 (91.3)	0.544	41 (52.6)	5 (33.3)	36 (57.1)	0.150
Orbital pain	34 (10.1)	4 (4.7)	30 (11.9)	0.062	36 (14.2)	2 (4.4)	34 (16.4)	**0.035**	10 (12.8)	1 (6.7)	9 (14.3)	0.677
Bone pain	111 (32.8)	19 (22.4)	92 (36.4)	**0.023**	80 (31.6)	19 (41.3)	61 (29.5)	0.160	25 (32.1)	3 (20)	22 (34.9)	0.362
Myalgia	199 (58.9)	41 (48.2)	158 (62.5)	**0.023**	133 (52.6)	24 (52.2)	109 (52.7)	>0.99	38 (48.7)	6 (40)	32 (50.8)	0.569
Headache	142 (42)	24 (28.2)	118 (46.6)	**0.003**	87 (34.4)	13 (28.3)	74 (35.8)	0.393	23 (29.5)	5 (33.3)	18 (28.6)	0.757
Rashes	98 (29)	15 (17.7)	83 (32.8)	**0.008**	119 (47)	18 (39.1)	101 (48.8)	0.256	53 (68)	7 (46.7)	46 (73)	0.067
Diarrhea	47 (14)	10 (11.8)	37 (14.6)	0.590	44 (18)	11 (23.9)	33 (15.9)	0.202	9 (12)	0	9 (14.1)	0.193
Petechial	43 (12.7)	8 (9.4)	35 (13.8)	0.350	47 (18.6)	8 (17.4)	39 (18.8)	>0.99	11 (14.1)	3 (20)	8 (12.7)	0.434
Warning signs[b]												
Abdomen pain/ tenderness, no. (%)	57 (17)	17 (20)	40 (15.8)	0.403	55 (21.8)	9 (19.6)	46 (22.2)	0.844	13 (16.7)	7 (46.7)	6 (9.5)	**0.002**
Persistent vomiting, no. (%)	64 (19)	29 (34.1)	35 (13.8)	<**0.001**	53 (21)	12 (26.1)	41 (19.8)	0.423	11 (14.1)	3 (20)	8 (12.7)	0.434
Clinical fluid accumulation												
Pleural effusion, no./No. (%)	35/259 (9.8)	18/71 (25.5)	17/188 (9.1)	**0.002**	21/186 (11.3)	10/40 (25)	11/146 (7.5)	**0.004**	7/57 (12.3)	4/14 (28.6)	3/43 (6.9)	0.054
Ascites, no./No. (%)	4/65 (6.2)	0/27 (0)	4/38 (10.5)	0.135	13/72 (18)	7/21 (33.3)	6/51 (11.8)	0.038	5/33 (15.1)	2/13 (15.4)	3/20 (15)	>0.99
Mucosal bleeding, no. (%)	33 (9.8)	14 (16.5)	19 (7.5)	**0.021**	42 (17)	15 (32.6)	27 (13)	**0.003**	16 (21)	7 (46.7)	9 (14.3)	**0.010**
Gastrointestinal bleeding	14 (4.1)	7 (8.2)	7 (2.8)	0.052	26 (10.3)	8 (17.4)	18 (8.7)	0.104	9 (11.5)	4 (26.7)	5 (7.9)	0.064
Gum bleeding	15 (4.4)	7 (8.2)	8 (3.2)	0.066	16 (6.3)	6 (13)	10 (4.8)	**0.049**	8 (10.3)	3 (20)	5 (7.9)	0.177
Hemoptysis	3 (0.9)	2 (2.4)	1 (0.4)	0.157	1 (0.4)	1 (2.3)	0	0.182	1 (1.3)	0	1 (1.6)	>0.99
Epistaxis	1 (0.3)	0	1 (0.4)	>0.99	2 (0.8)	0	2 (1)	>0.99	0	0	0	–
Other bleeding	2 (0.6)	0	2 (0.8)	>0.99	1 (0.4)	0	1 (0.5)	>0.99	0	0	0	–
Increase in hematocrit (>20%) concurrent with rapid decrease in platelet count, no. (%)	2 (0.6)	1	1 (0.4)	>0.99	0	0	0	–	1 (1.3)	0	1 (1.6)	>0.99

(*continued on next page*)

Table 1 (*continued*)

Variable	Febrile phase			*P* (A vs. B)	Critical phase			*P* (C vs. D)	Recovery phase			*P* (E vs. F)
	Total (N = 338)	Elderly (N = 85) (A)	Non-elderly (N = 253) (B)		Total (N = 253)	Elderly (N = 46) (C)	Non-elderly (N = 207) (D)		Total (N = 78)	Elderly (N = 15) (E)	Non-elderly (N = 63) (F)	
Laboratory characteristics												
Mean WBC (range) ($\times 10^9$ cells/L) (no.)	4.1 (0.6–12.6) (n = 329)	4.9 (1.6–12.6) (n = 83)	3.9 (0.6–11) (n = 246)	**<0.001**	3.6 (0.7–28) (n = 249)	4.3 (1.6–13.9) (n = 46)	3.4 (0.7–28) (n = 203)	**0.002**	4.3 (1.5–11.2) (n = 76)	5.6 (1.7–9.1) (n = 15)	4.0 (1.5–11.2) (n = 60)	**0.027**
Mean hematocrit (range) (%) (no.)	40.4 (21.4–58) (n = 329)	40.1 (24.5–50.4) (n = 83)	40.5 (21.4–58) (n = 245)	0.649	41.6 (24.7–52.4) (n = 247)	41 (31.2–49.4) (n = 46)	41.7 (24.7–52.4) (n = 201)	0.293	41.8 (25.3–53.4) (n = 76)	42.1 (26.2–52.1) (n = 15)	41.7 (25.3–53.4) (n = 61)	0.389
Mean platelet count (range) ($\times 10^9$ cells/L) (no.)	123.2 (3.0–403) (n = 328)	102.2 (5–242) (n = 83)	130.2 (3–403) (n = 246)	**<0.001**	84.1 (5.0–269) (n = 247)	48.4 (5–175) (n = 46)	92.3 (6–269) (n = 201)	**<0.001**	79.8 (5.0–307) (n = 76)	43.5 (5–120) (n = 15)	88.8 (10–307) (n = 61)	**0.002**
Mean AST (range) (U/L) (no.)	84.6 (11–2477) (n = 263)	133 (25–2477) (n = 62)	69.7 (11–577) (n = 201)	**<0.001**	110 (23–1394) (n = 183)	144.3 (34–451) (n = 30)	104.1 (23–1394) (n = 153)	**0.006**	151 (29–1186) (n = 57)	148 (40–397) (n = 10)	152.4 (29–1186) (n = 47)	0.564
Mean ALT (range) (U/L) (no.)	60.3 (9–1015) (n = 272)	82.4 (16–1015) (n = 67)	53.1 (9–368) (n = 205)	**<0.001**	78.1 (10–724) (n = 200)	91.1 (10–338) (n = 39)	74.9 (10–724) (n = 161)	**0.029**	101.7 (5–641) (n = 64)	82.1 (34–171) (n = 13)	106.7 (5–641) (n = 51)	0.770

[a] Based on the World Health Organization 2009 dengue classification scheme.[1]

[b] An individual patient might have more than one symptom/sign.

AST = aspartate aminotransferase; ALT = alanine aminotransferase; WBC = white blood cell count.

Bold formatting indicates statistical significance.

Description of severe dengue cases

Severe dengue was found in 27 patients (mean age, 66.4 ± 12.8 years; 19 [70.4%] elderly and 15 [55.6%] males). An individual patient might have more than one manifestation of severe dengue. Severe plasma-leak-associated shock/respiratory distress and severe bleeding were each found in 9 (33.3%) patients, and severe organ impairment in 19 (70.4%). The three leading symptoms other than fever at hospital presentations were myalgia (55.6%), persistent vomiting (51.9%) and gastrointestinal bleeding (44.4%). As for laboratory findings at hospital presentations, leukocytosis (white blood cell count $> 10 \times 10^9$ cells/L) was seen in 4 (14.8%) patients; the mean hematocrit was 39.5% (range, 21.9—52.1%) and mean platelet count 60.3 (range, 5—190) $\times 10^9$ cells/L.

Comparisons between patients with severe and non-severe dengue cases are shown in Table 2. Severe dengue patients were significantly older ($P < 0.001$), and had higher incidences of diabetes mellitus ($P = 0.008$), hypertension ($P < 0.001$) and chronic kidney disease ($P = 0.004$) as well as higher frequencies of abdomen pain ($P = 0.009$), persistent vomiting ($P < 0.001$) and gastrointestinal bleeding ($P < 0.001$).

Severe dengue was found in all WHO-proposed dengue clinical phases (Table 3). Specifically, severe dengue developed in 12 (1.8%) patients (median age, 71 years) in their febrile, 11 (1.6%) (median age, 69 years) in their critical, and 4 (0.6%) (median age, 68.5 years) in their recovery phases. There were no significant differences in the occurrence of severe dengue between (i) febrile and critical phases, (ii) critical and recovery phases, and (iii) febrile and recovery phases.

Comparison of clinical and laboratory characteristics between (i) febrile and critical, (ii) critical and recovery, and (iii) febrile and recovery phases of acute dengue illness (Table 1)

(i) Febrile (n = 338) vs. critical (n = 253)phases

Patients in critical phase had significantly higher frequencies of rash ($P < 0.001$), ascites ($P = 0.040$), mucosal bleeding ($P < 0.001$), gastrointestinal bleeding ($P = 0.004$); lower white blood cell count ($P < 0.001$) and platelet count ($P < 0.001$); higher hematocrit ($P = 0.002$), AST ($P < 0.001$) as well as ALT ($P < 0.001$) levels.

(ii) Critical (n = 253)vs. recovery (n = 78) phases

Significantly lower frequency of fever ($P < 0.001$) and higher frequency of rashes ($P = 0.002$); higher white blood cell count ($P = 0.001$), AST ($P = 0.046$) and ALT ($P = 0.006$) levels were noted in patients in the recovery phase than those in the critical phase of acute dengue illness.

(iii) Febrile (n = 338)vs. recovery (n = 78) phases

Table 2 Comparisons of clinical characteristics between severe and non-severe dengue cases.

Variable	Overall (N = 669)	Severe dengue (N = 27) (A)	Non-severe dengue (N = 642) (B)	*P* (A vs. B)
Demographic features and outcome				
Mean age (±SD), year	49.9 (±16.7)	66.4 (±12.8)	48.65 (±16.6)	**<0.001**
Age ≥65 years, no. (%)	146 (21.8)	19 (70.4)	127 (19.8)	**<0.001**
Male, no. (%)	341 (51)	15 (55.6)	326 (50.8)	0.697
Time lapse (day) from onset of dengue to hospital presentation, mean (range),	3.8 (1—15)	3.7 (1—7)	3.8 (1—15)	0.982
Comorbid condition[a], no. (%)				
Diabetes mellitus	95 (14.2)	9 (33.3)	86 (13.4)	**0.008**
Hypertension	165 (24.7)	19 (70.4)	146 (22.7)	**<0.001**
Chronic kidney disease	17 (2.6)	4 (14.8)	13 (2.0)	**0.004**
Malignancy	24 (3.6)	0 (0)	24 (3.7)	0.617
Fatality, no. (%)	2 (0.3)	2 (7.4)	0 (0)	**0.002**
Symptom/sign[b], no. (%)				
Fever	593 (92.8)	23 (85.2)	570	0.534
Orbital pain	80 (12.5)	2 (7.4)	78	0.76
Bone pain	216 (33.8)	8 (29.6)	208	0.837
Myalgia	370 (57.9)	15 (55.6)	355	1
Headache	252 (39.4)	10 (37.0)	242	1
Rashes	270 (42.3)	6 (22.2)	264	0.07
Diarrhea	100 (15.6)	5 (18.5)	95	0.582
Petechiae	101 (15.8)	5 (18.5)	96	0.584
Abdomen pain or tenderness, no. (%)	125 (19.6)	11 (40.7)	114	**0.009**
Persistent vomiting, no. (%)	128 (20.0)	14 (51.9)	114	**<0.001**
Gastrointestinal bleeding	49 (7.7)	12 (44.4)	37	**<0.001**

[a] An individual patient might have more than one comorbidity.
[b] Data for the time of hospital presentations.
Bold formatting indicates statistical significance.

Table 3 Severe dengue in elderly (≥65 years; N = 146) and younger (18–64 years; N = 523) adults in the WHO-proposed febrile (days 1–3), critical (days 4–6), and recovery (days ≥ 7) phases.[a]

Variable	Febrile phase			*P*	Critical phase			*P* (C vs. D)	Recovery phase			*P* (E vs. F)
	Total	Elderly (A)	Non-elderly (B)	(A vs. B)	Total	Elderly (C)	Non-elderly (D)		Total	Elderly (E)	Non-elderly (F)	
Severe dengue, no. (%)	12 (1.8)	10 (6.9)	2 (0.4)	**<0.001**	11 (1.6)	7 (4.8)	4 (0.8)	**0.003**	4 (0.6)	2 (1.4)	2 (0.9)	0.209
Severe plasma leakage with shock or respiratory distress, no. (%)	5 (0.8)	4 (2.7)	1 (0.2)	**0.009**	4 (0.6)	4 (2.7)	0	**0.002**	0	0	0	–
Severe bleeding, no. (%)	4 (0.6)	4 (2.7)	0	**0.002**	3 (0.5)	0	3 (0.6)	**>0.99**	2 (0.3)	1 (0.7)	1 (0.2)	0.389
Severe organ impairment,[b] no. (%)	9 (1.4)	8 (5.9)	1 (0.2)	**<0.001**	8 (1.2)	5 (3.4)	3 (0.6)	**0.015**	2 (0.3)	1 (0.7)	1 (0.2)	0.389

[a] Based on the World Health Organization 2009 dengue classification scheme[1]; an individual patient might have more than one manifestation of severe dengue.
[b] See text for details.
Bold formatting indicates statistical significance.

Compared to patients in febrile phase, patients in recovery phase had significantly lower frequency of fever ($P < 0.001$); higher frequencies of skin rash ($P < 0.001$), mucosal bleeding ($P = 0.001$) and gastrointestinal bleeding ($P = 0.023$); lower platelet count ($P < 0.001$); higher hematocrit ($P = 0.006$), AST ($P < 0.001$) and ALT ($P < 0.001$) levels.

Comparison of clinical and laboratory characteristics between the elderly and non-elderly adults (Table 1)

(i) Elderly (n = 85) vs. non-elderly (n = 253) in the febrile phase

Elderly patients had significantly lower frequencies of bone pain ($P = 0.023$), myalgia ($P = 0.023$), headache ($P = 0.003$) and rash ($P = 0.008$); higher frequencies of persistent vomiting ($P < 0.001$), pleural effusion ($P = 0.002$) and mucosal bleeding ($P < 0.021$); higher white blood cell count ($P < 0.001$), AST ($P < 0.001$) and ALT ($P < 0.001$) levels; lower platelet count ($P < 0.001$).

(ii) Elderly (n = 46) vs. non-elderly (n = 207) in the critical phase.

Elderly patients had significantly lower frequency of orbital pain ($P = 0.035$); higher frequency of pleural effusion ($P = 0.004$), ascites ($P = 0.038$), mucosal bleeding ($P = 0.003$) and gum bleeding ($P = 0.049$); higher white blood cell count ($P = 0.002$), AST ($P = 0.006$) and ALT ($P = 0.029$); lower platelet count ($P < 0.001$).

(iii) Elderly (n = 15) vs. non-elderly (n = 63) in the recovery phase

Elderly patients had significantly higher frequency of abdomen pain ($P = 0.002$) and mucosal bleeding ($P = 0.010$); higher white blood cell count ($P = 0.027$) and lower platelet count ($P = 0.002$).

Comparison of the severe dengue between elderly and non-elderly adults (Table 3)

Significantly higher percentages of elderly patients experienced severe dengue in the febrile ($P < 0.001$) and critical phases ($P < 0.003$) of dengue illness.

Discussion

While dengue is complex in its manifestations, management is relatively simple.[1,2] Triage and management at the primary and secondary care levels where patients are first seen and evaluated are critical in determining the clinical outcomes.[1,2,30] Different clinical dengue phases were put forward by the WHO as a framework for guidance to dengue triage and management for frontline medical personnel, emphasizing important clinical and laboratory features in each of these clinical phases.[1,2] For example, nonspecific symptoms/signs found in viral infections such as fever, headache, myalgia and rashes are stressed in the febrile phase, whereas shock and other symptoms/signs suggesting severe dengue are underlined in the critical phase.[1,2] It is noteworthy that our data clearly show that the nonspecific symptoms were possibly found throughout the clinical

course, irrespective of the clinical phases. Our data also indicate that skin rash in dengue adults emerged from the febrile phase with progressive increase in incidence throughout the clinical course, reaching its height at the recovery phase.

In addition to showing clinical and laboratory data in dengue adults in general, the age-stratified analyses demonstrated the difference in dengue clinical and laboratory manifestations between elderly and younger adults. This is not surprising as the dengue manifestations result from a complex immune reaction with the sophisticated interplay between the host and the culprit virus.[6,20–22] These data potentially help clinicians be vigilant to possible dengue in adults in general and in the elderly in particular, alerting to the stereotyped trap of dengue symptoms/signs and timing of emergence of these symptoms/signs based on the WHO dengue clinical-phase framework.[2] Early diagnosis of dengue is important for starting close monitor of the patient and timely delivering necessary management in case of deterioration, and early notification of dengue cases is crucial for identifying an outbreak and initiating an early response.

Of note, in what was supposed to be recovery phase (≧7 days), persistent fever was found in approximately half of patients, and severe dengue developed in 4 (0.6%) patients in this serial. These data suggest that the clinical-phase framework proposed by the WHO mainly based on observations of pediatric patients not always be valid for dengue adults.[5] Furthermore, >90% of our patients were experiencing persistent fever in critical phase, which was in disagreement with the description by the WHO dengue scheme that defervescence was commonly found in the critical phase.[1,5]

In addition to the elevation of serum AST and ALT, which has been well recognized in dengue patients,[1,31–34] our data show that AST and ALT values were significantly higher during recovery phase. Typically, transaminase levels began to increase from the early stage of dengue and peaked during the second week of the dengue illness.[34] In most dengue patients, serum AST and ALT are slightly elevated; under supportive care, one can always anticipate a full recovery of the liver function in dengue patients, while development of hepatic failure is rare.[1,32–35] As were found in previous studies,[36,37] these liver enzyme levels were increased proportionately with dengue severity, but there was no association between transaminase levels and clinical outcomes in dengue patients.[37]

In consistent with previous reports,[1,3,6] our data demonstrated that diabetes mellitus, hypertension and chronic kidney disease were risk factors for development of severe dengue; abdominal pain, persistent vomiting and gastrointestinal bleeding, the previously reported warning signs of severe dengue, were frequently found in severe dengue.

In addition to showing that a variety of bleedings, ranging from subcutaneous bleeding to gastrointestinal bleeding, occurred throughout the clinical courses as were described elsewhere,[1–3] our data indicate that gastrointestinal bleeding significantly commonly occurred in both the WHO-proposed critical and recovery phases, and in agreement with other reports,[38,39] mostly occurred on day 4. As thrombocytopenia implicates higher risk for hemorrhagia,[40] the progressive thrombocytopenia evolved from the WHO-proposed febrile phase toward the recovery phase in this serial highlights the importance a close monitor of patients' conditions throughout the clinical dengue course so that necessary management could be delivered in case of massive bleedings.

In consistent with other series,[29,41,42] our report indicates that elderly dengue patients were at higher risk of development of DHF/severe dengue, and noteworthy, our data highlights that a significant number of the elderly developed severe dengue at the early clinical stage where it was supposed to be the WHO-proposed dengue febrile phase, suggesting clinicians should always keep vigilant eye on the potential development of severe dengue no matter how early the diagnosis of dengue was made in elderly patients, so that timely management could be started as necessary.

This study has a number of limitations. First, the study was conducted at a single medical center, and the severity of dengue may be biased by referral pattern. Second, as a retrospective study, missing laboratory data were inevitable. Third, we did not have information concerning primary/secondary dengue infections in our patients. Fourth, it is likely that different dengue serotypes were responsible for dengue in the included patients. Fifth, our data about the frequencies of symptoms/signs of dengue in different clinical phases at patients' hospital presentations may be biased by the possibility that the majority of patients who got dengue with mild or no symptoms did not seek medical help from the hospital. In summary, our study provides a comprehensive depiction of the clinical and laboratory features found in dengue adults at their hospital presentations when they were evaluated based on the WHO-proposed dengue framework. The clinical courses of dengue were highly heterogeneous. A small number of patients developed severe dengue when they were supposed to be in the WHO-proposed recovery phase. Elderly dengue patients had less classical dengue symptoms such as bone pain, myalgia, and headache, yet were at higher risk for development of severe dengue, and the severe dengue might develop during their early clinical dengue course. In conclusion, data shown in this study are helpful in alerting clinicians to dengue in adults in general, and in the elderly in particular, and are also helpful in mapping out dengue management strategy for adult populations.

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