

## BACKGROUND

Dengue virus infection has become an emerging infectious disease worldwide and the incidence has increased 30-fold in the last 50 years with increasing geographic expansion and emerging in new countries. Currently, there is an increasing number of adult patients diagnosed with dengue virus infection. Dengue virus infection is a systemic disease, has dynamic change in clinical phase, and appears to be difficult to predict clinical evolution. Dengue hemorrhagic fever (DHF) is a life-threatening clinical condition of dengue fever (DF). Early recognition of cases with high risk to develop DHF helps for clinician's decision in the intensity of monitoring and choices of management plan. This study aimed to determine predictors of DHF in adult patients presented with DF.

## METHODS

A case-control study was conducted among adult patients presented with DF in Ramathibodi Hospital, a medical-school hospital in Bangkok, Thailand, between January 2005 and December 2012. Patients were categorized into DF group and DHF group using case definition of WHO dengue classification 1997 (Table 1). Clinical and laboratory parameters were compared between the two groups from day 2 to day 6 of fever.

Table 1. The definition of dengue fever and dengue hemorrhagic fever (WHO 1997)

Probable dengue fever	Dengue hemorrhagic fever
Acute febrile illness with 2 of the following	Acute febrile illness with 4 of the following
- headache	1. fever
- retro-orbital pain	2. hemorrhagic manifestation (positive tourniquet test, petechiae/ecchymoses, mucosa bleeding),
- myalgia	3. thrombocytopenia (platelet count < 100,000 cells/mm <sup>3</sup> )
- arthralgia	4. evidence of plasma leakage
- rash	- hemoconcentration ≥ 20 % above baseline
- hemorrhagic manifestation	- pleural effusion or ascites by physical examination or imaging study
- leucopenia	- hypoalbuminemia by serum albumin ≤ 35 g/L
If plus laboratory confirm = confirmed dengue fever	- hypocholesterolemia by serum cholesterol ≤ 100 mg/dL

## RESULTS

Of 197 patients, 111 were in DF group and 86 were in DHF group. The median (range) age was 23 (15-71) years old. DHF group had significantly older median (IQR) age [28 (20-41) vs. 21 (17-29) years,  $p < 0.001$ ] and a higher proportion of female gender (64% vs. 41%,  $p = 0.002$ ) than DF group. Of all, 71% had positive tourniquet test and 42% had laboratory-confirmed diagnosis of Dengue virus infection (positive NS1, Dengue IgM, Dengue IgG, and/or PCR). Bleeding complication (GI bleeding, hemoptysis, epistaxis, bleeding per gum, hypermenorrhea) was observed in 8%. Table 2 shows predictor parameters between the two groups.

Table 2. Predictor parameters in 197 study patients\*

Predictor parameters	DF (n = 111)	DHF (n = 86)	P value
Day out of fever (% of patients)			0.643
Day 3	0	2.3	
Day 4	6.7	11.6	
Day 5	28.9	32.6	
Day 6	55.6	48.8	
Day 7	8.9	4.7	
Hematocrit baseline (%), mean ± SD	39.5 ± 4.4	38.1 ± 4.2	0.134
Hematocrit maximum (%), mean ± SD	43.8 ± 4.7	45.4 ± 6.3	0.053
Hematocrit rising (%rising), median (IQR)	7.1 (1.3-12.6)	17.1 (6.3-22.8)	<0.001
Platelet (x10 <sup>3</sup> /mm <sup>3</sup> ), median (IQR)			
Day 2	162 (141-199)	164 (99-178)	0.554
Day 3	140 (100-156)	101 (58-135)	0.002
Day 4	96 (73-129)	63 (40-89)	<0.001
Day 5	74 (51-105)	43 (20-68)	<0.001
Day 6	57 (31-86)	29 (18-52)	<0.001
Aspartate ST (U/L), median (IQR)			
Day 2	31 (23-57)	86 (42-432)	0.043
Day 3	80 (53-138)	136 (85-253)	0.075
Day 4	84 (55-155)	206 (103-494)	0.003
Day 5	127 (78-185)	217 (130-463)	0.006
Day 6	231 (160-418)	256 (125-529)	0.847
ALT (U/L), median (IQR)			
Day 2	42 (31-69)	128 (51-375)	0.513
Day 3	63 (43-146)	120 (69-214)	0.193
Day 4	76 (36-138)	140 (116-269)	0.008
Day 5	96 (69-140)	162 (69-283)	0.082
Day 6	157 (91-410)	162 (109-353)	0.934
Serum albumin, (g/L), median (IQR)			
Day 2	42.8 (41.2-44.5)	34.9 (29.3-41.8)	0.165
Day 3	41.5 (38.8-43.4)	34.6 (32.1-40.8)	0.070
Day 4	40.4 (39.0-42.3)	33.7 (31.7-35.3)	<0.001
Day 5	38.1 (36.5-40.4)	32.4 (28.1-34.2)	<0.001
Day 6	41.9 (41.0-42.8)	31.3 (28.4-33.0)	<0.001

\*White blood cell count, alkaline phosphatase, total protein, creatinine, absolute values and changes, were not different between the two groups, from day 2 to day 6 ( $p > 0.05$ )

Platelet counts were significantly different between the two groups from day 3 to day 6, in which platelet count in DHF group was lower than DF group ( $p < 0.05$ ). Liver function test revealed that alanine transaminase (ALT) level on day 4 was significantly higher in DHF group.

Univariate and multivariate analysis for factors associated with DHF among 197 patients with Dengue viral infection are shown in Table 3. From multivariate analysis of factors associated with DHF, we identified 4 independent predicting factors for DHF: age > 25 years, female gender, platelet day 3 < 100,000/mm<sup>3</sup>, and ALT day 4 > 120 IU/L.

Table 3. Univariate and Multivariate analysis for factors associated with DHF among 197 patients with Dengue viral infection

Factors	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	Adjusted OR	95% CI	P value
Age > 25 years	2.617	1.460-4.690	0.001	6.513	1.110-38.203	0.032
Female gender	2.602	1.456-4.651	0.001	7.669	1.388-42.362	0.019
Platelet day 3 < 100,000/mm <sup>3</sup>	4.014	1.453-11.088	0.007	3.807	1.311-11.058	0.014
AST day 4 > 120 IU/L	4.411	1.282-15.174	0.019	-	-	-
ALT day 4 > 120 IU/L	8.333	2.238-31.033	0.002	13.557	2.241-82.252	0.005
Albumin day 4 < 32 g/dL	1.313	0.980-1.757	0.109	-	-	-

## CONCLUSION

DHF is common among adult patients with dengue virus infection. We proposed four clinical predicting factors for DHF in adults that may help clinicians to plan appropriate management for patients with dengue virus infection.