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Prognostic Indicators for Dengue Infection Severity

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Abstract

Background: Symptomatic dengue infection can be classified into 3 patterns based on their severity; dengue fever (DF), dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). In clinical practice, the diagnosis and management are based on clinical findings and abnormal initial laboratory tests. We conducted the present study to explore a set of parameters, preferable routine, or at least easy to investigate, that could be used as indicators for dengue infection severity.

Methods: A retrospective cohort study was conducted in three university-affiliated hospitals, one general hospital and two referral hospitals, in the northern part of Thailand. Patients were grouped into the three severity categories (DF, DHF, and DSS), using modified WHO criteria. Pre-defined prognostic indicators were compared. The prognostic indicators for dengue severity were analyzed by a multivariable polytomous logistic regression and presented with odds ratios.

Results: From 777 patients overall, 391 were classified as DF, 296 with DHF, and 90 with DSS. The characteristics that increased the risk of DHF were; age > 6 year (OR = 1.85), hepatomegaly (OR = 3.49), any bleeding episodes (OR = 1.43), white cell count > 5,000/μL (OR = 1.80), and platelet ≤ 100,000/μL (OR = 3.72). The characteristics that increase the risk of DSS were; hepatomegaly (OR = 43.44), any bleeding episodes (OR = 5.58), pulse pressure ≤ 20 mmHg (OR = 19.09), SBP < 90 mmHg (OR = 2.45), hematocrit > 40% (OR = 1.88), white cell count > 5,000/μL (OR = 2.36), and platelet ≤ 100,000/μL (OR = 10.60).

Conclusions: The severity of dengue infection is significantly associated with some routine clinical parameters. These parameters may be used to develop a future scoring system to predict and manage dengue infection severity early in the course of the illness.

Keywords: Dengue infection; Dengue hemorrhagic fever; Dengue shock syndrome; Severity; Prognostic indicators; Clinical risk; Multivariable analysis

Introduction

Most of dengue infections are asymptomatic. Those with symptoms can be classified into 3 patterns, based on their severity; undifferentiated fever, dengue fever (DF) and dengue hemorrhagic fever (DHF) which if accompanied by shock, is called dengue shock syndrome (DSS) [1].

In clinical practice, the diagnosis and management are based on clinical findings and abnormal initial laboratory tests [2]. Other laboratory tests may be requested to confirm case, as being used in research. These tests take several days to weeks for the results and are not used in routine practice. They are therefore used mainly for epidemiological purposes [3, 4].

The causes of mortality in dengue infection are from prolonged shock, massive bleeding and fluid overload. The main problem leading to poor prognosis or death is not being diagnosed when presenting in critical conditions at the hospitals [5, 6].

Clinical risks and laboratory tests have been studied to forecast the severity of infection. These included gender [7], younger age [7], presence of hepatomegaly [8], abdominal pain [9], lethargy, cold hands and feet [10], abnormal bleeding episodes [11, 12], obesity or over-weight (in children) [9, 13], malnourishment [14], type 2 dengue infection [13], secondary infection [11], presence of ascites [8], plural effusion [8], leucopenia (< 4,000/μL) [8], thrombocytopenia [10], hemo-concentration [11], rising SGOT and/or SGPT [12, 15], prolonged PTT [16], prolonged PT [17], positive

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Table 1. Grading Dengue Infection Severity (Modified WHO 1997)

DF/DHF	Grade	Symptoms	Laboratory
DF*		Fever with two or more of the following signs: headache, retro-orbital pain, myalgia, arthralgia plus positive tourniquet test	Leucopenia occasionally Thrombocytopenia, may be present, no evidence of plasma loss
DHF	I	Above signs plus positive tourniquet test	Thrombocytopenia ≤ 100,000/ μL, hematocrit rise ≥ 20%
DHF	II	Above signs plus spontaneous bleeding	Thrombocytopenia ≤ 100,000/ μL, hematocrit rise ≥ 20%
DHF	III**	Above signs plus circulatory failure (weak pulse, hypotension, restlessness)	Thrombocytopenia ≤ 100,000/ μL, hematocrit rise ≥ 20%
DHF	IV**	Profound shock with undetectable blood pressure and pulse	Thrombocytopenia ≤100,000/ μL, hematocrit rise ≥ 20%

DF: dengue fever; DHF: dengue hemorrhagic fever; *Modified WHO criteria; **DHF Grade III and IV are also called as dengue shock syndrome (DSS).

of the D-dimer test [18], and gallbladder wall thickening (measured by ultrasound) [19]. It is obvious that many parameters above are not used as routine practice in general hospitals. Many parameters require days to weeks for final reports. Some reports have very few sample sizes and some are descriptive or case series.

We conducted the present study to explore a set of parameters, preferable routine, or at least easy to investigate, that could be used as indicators for dengue infection severity. These indicators may be used to forecast dengue infection severity at the time the patients arrive at out-patient or emergency departments of the hospitals.

Materials and Methods

Patients

Three university-affiliated hospitals were selected to represent the study domain, one general hospital (in Kamphaeng Phet) and two referral hospitals (in Nakorn Sawan and in Uttaradit). Medical files of patients admitted between 2007 and 2010 were searched under the following ICD-10s; A90-Dengue fever, A91-Dengue hemorrhagic fever, and A910-Dengue hemorrhagic fever with shock.

Criteria for dengue severity

The severity of dengue infection is classified into different grades using modified WHO criteria [1] (Table 1).

Prognostic indicators

Patient characteristics of interest included: 1). Demographic: gender and age; 2). Mode of Presentation: presence of hepatomegaly, headache, myalgia, vomiting, cough, abdominal pain, rash, pleural effusion, petechiae, and any bleeding episodes; 3). Hemodynamic: pulse pressure, SBP (systolic blood pressure), and DBP (diastolic blood pressure); 4). Hematological: hematocrit, hemoglobin, white cell count, lymphocytes, neutrophils, and platelet; 5). Biochemical: SGOT (serum glutamic oxaloacetic transaminase), SGPT (serum glutamic pyruvic transaminase), PT (prothrombin time), and PTT (partial thromboplastin time).

Data analysis

Different distribution of patient characteristics among the three severity categories (DF, DHF, and DSS) was analyzed by exact probability test, analysis of variance (ANOVA), or ANOVA by rank based on types of variables. Complete data were used to screen for selected important parameters. Significant parameters were analyzed by the multivariable polytomous logistic regression to identify a set of significant characteristics associated with severity. Multiple imputation techniques were applied to clinical variables with missing values in the last step of analysis.

Ethical approval

The study protocol was approved by The Research Ethics

Table 2. Demographic and Clinical Profiles by Types of Dengue Infection

Patient characteristics	DF (n = 391)	DHF (n = 296)	DSS (n = 90)	P-value*
	Mean ± SD	Mean ± SD	Mean ± SD	
Demographic				
Male (n, %)	185 (47.3)	153 (51.7)	38 (42.2)	0.247
Age (year)	9.5 ± 3.4	10.1 ± 3.1	9.0 ± 3.5	0.009
Mode of presentation				
Hepatomegaly (n, %)	8 (2.1)	26 (8.8)	55 (61.1)	< 0.001
Headache (n, %)	228 (58.3)	145 (49.0)	35 (38.9)	< 0.001
Myalgia (n, %)	84 (21.5)	30 (10.1)	12 (13.3)	0.001
Vomiting (n, %)	244 (62.4)	216 (73.0)	56 (62.2)	0.009
Cough (n, %)	120 (30.7)	94 (31.8)	32 (35.6)	0.751
Abdominal pain (n, %)	160 (40.9)	181 (61.2)	60 (66.7)	< 0.001
Rash (n, %)	166 (42.5)	132 (44.6)	26 (28.9)	0.026
Pleural effusion	0 (0)	20 (6.8)	34 (37.8)	< 0.001
Petechiae (n, %)	27 (6.9)	26 (8.8)	14 (15.6)	0.039
Any bleeding episodes (n, %)	73 (18.7)	80 (27.0)	51 (56.7)	< 0.001
Hemodynamic				
SBP (mmHg)	97.0 ± 9.2	96.9 ± 10.1	91.3 ± 10.3	< 0.001
DBP (mmHg)	58.4 ± 7.7	58.2 ± 8.6	58.6 ± 8.4	0.356
Pulse pressure (mmHg)	33.1 ± 6.7	32.1 ± 7.6	24.0 ± 7.7	< 0.001
Hematological				
Hematocrit (%)	38.8 ± 4.5	40.5 ± 4.8	42.4 ± 5.4	< 0.001
Hemoglobin (g/dl)	12.7 ± 1.5	13.4 ± 1.5	14.1 ± 1.8	< 0.001
White cell count (/μL)**	3,348.0 ± 1.6	3,737.5 ± 1.7	4,773.4 ± 1.7	< 0.001
Lymphocytes (%)	44.9 ± 17.3	40.8 ± 15.7	40.0 ± 16.3	< 0.001
Neutrophils (%)	44.7 ± 18.8	49.5 ± 18.1	48.9 ± 17.6	< 0.001
Platelet (/μL)**	106,084.3 ± 1.8	62,533.8 ± 2.2	36,074 ± 2.3	< 0.001
Biochemical				
SGOT (U/L)**	84.2 ± 2.4	158.1 ± 2.4	219.4 ± 3.7	< 0.001
SGPT (U/L)**	42.1 ± 2.3	60.6 ± 2.4	78.7 ± 3.7	0.005
PT (sec)	12.0 ± 1.5	12.1 ± 1.8	15.5 ± 9.5	0.159
PTT (sec)	30.4 ± 5.4	42.0 ± 10.0	44.7 ± 12.3	0.011
Case management				
Inbound referral (n, %)	43 (11.0)	78 (26.4)	48 (53.3)	< 0.001
Discharged				
Alive (n, %)	391 (100.0)	296 (100.0)	88 (97.8)	0.013
Outbound referral (n, %)	0 (0)	0 (0)	2 (2.2)	0.013
In hospital dead (n, %)	0 (0)	0 (0)	0 (0)	0.013

Dengue fever (DF); dengue hemorrhagic fever (DHF); dengue shock syndrome (DSS); *P-value from exact probability test or analysis of variance (ANOVA) or ANOVA by rank; **geometric mean and standard deviation (SD); SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase; PT: prothrombin time; PTT: partial thromboplastin time.

Table 3. Multivariable Odds Ratios (OR) and 95% Confidence Interval (CI) of Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS), Compared to Dengue Fever (DF)

Patient characteristics	DHF (n = 296)			DSS (n = 90)		
	OR*	95%CI	P-value	OR*	95%CI	P-value
Age > 6 year	1.85	1.35 - 2.54	< 0.001	1.80	0.95 - 3.41	0.071
Hepatomegaly	3.49	2.01 - 6.06	< 0.001	43.44	22.71 - 83.09	< 0.001
Any bleeding episodes	1.43	1.10 - 1.85	0.007	5.58	3.43 - 9.10	< 0.001
PP ≤ 20 mmHg	1.22	0.68 - 2.19	0.501	19.09	9.64 - 37.80	< 0.001
SBP < 90 mmHg	1.05	0.77 - 1.43	0.778	2.45	1.41 - 4.25	0.001
Hematocrit > 40%	1.06	0.84 - 1.34	0.600	1.88	1.16 - 3.05	0.010
WBC > 5,000/μL	1.80	1.39 - 2.33	< 0.001	2.36	1.44 - 3.86	0.001
Platelet ≤ 100,000/μL	3.72	2.97 - 4.66	< 0.001	10.60	4.98 - 22.55	< 0.001

*Odds ratio from multivariable polytomous logistic regression, compare to dengue fever (DF); PP: pulse pressure; WBC: white blood cell count.

Committee, Faculty of Medicine, Chiang Mai University, and the research ethics committee of the three hospitals.

Results

There were 777 patients overall, 391 with DF, 296 with DHF, and 90 with DSS. By univariable analysis, the three severity groups were similar in gender, age, presence of vomiting, cough, rash and SBP. The characteristics that were different by severity categories were; hepatomegaly, headache, myalgia, abdominal pain, pleural effusion, petechiae, any bleeding episodes, SBP, pulse pressure, hematocrit, hemoglobin, white cell count, lymphocytes, neutrophils, platelet, SGOT, SGPT, PT, and PTT (Table 2).

Under multivariable polytomous logistic regression, characteristics that increased the risk of DHF were; age > 6 year (OR = 1.85), hepatomegaly (OR = 3.49), any bleeding episodes (OR = 1.43), white cell count > 5,000/μL (OR = 1.80), and platelet ≤ 100,000/μL (OR = 3.72). The characteristics that increase the risk of DSS were; hepatomegaly (OR = 43.44), any bleeding episodes (OR = 5.58), pulse pressure ≤ 20 mmHg (OR = 19.09), SBP < 90 mmHg (OR = 2.45), hematocrit > 40% (OR = 1.88), white cell count > 5,000/μL (OR = 2.36), and platelet ≤ 100,000/μL (OR = 10.60) (Table 3).

Discussion

Demographic

Some previous studies reported more risk of shock and death in females [7, 20], due to more health seeking behavior to traditional practitioners [21]. Immune responses in females may be more sensitive to cytokines secretion, affecting higher degree of plasma leakage [21, 22]. However, our study and one other study [23] did not find gender as a risk of dengue infection severity.

Patients > 6 years were at risk for DHF and DSS in some studies [8, 9] from many factors such as serological coverage and mutation [24]. It was observed that children < 10 years are more prone to increased vascular permeability, leading to shock [9, 22].

Mode of presentation

Hepatomegaly was a strong risk factors in our study, similar to many studies in the past [10, 25]. Although moderate liver enlargement is a normal response to dengue infection [26], it is more associated with DHF and DSS compared to DF [27, 28].

Abdominal pain was reported as another prognostic factor [9, 10, 25]. It could be caused by gastrointestinal bleeding

and/or hepatomegaly. Other studies proposed that during the shock or pre-shock state, blood supply to visceral organs was reduced causing tissue hypoxia followed by abdominal pain [9]. This was not found in our study and one other study [29].

Pleural effusion was reported in some studies [8, 12, 30, 31], as it was found most commonly in dengue infection, associated with plasma leakage, leading to hypovolemic shock [1]. This was not found in our study.

In our and many studies, any bleeding episodes were also a prognostic factor [8, 11, 12]. This is associated with thrombocytopenia found in severe dengue infection. Platelet < 50,000/μL is associated with severe bleeding [32]. Bleeding may also caused by platelet dysfunction, vasculopathy and/or coagulopathy related to severe bleeding which may lead to death [33]. However some study did not find such relationship [9].

Hemodynamic

As expected, SBP < 90 mmHg and pulse pressure ≤ 20 mmHg are prognostic factors for DSS [34, 35]. WHO has used lowered SBP or narrow pulse pressure as criteria to classify dengue infection into different severity grades [1].

Hematological

Hematocrit > 40% is a prognostic factor for dengue infection severity particularly DSS, confirming the findings from many studies [10, 12, 28]. Vasculopathy in dengue infection causes increased vascular permeability, leading to hemoconcentration and shock [33, 36]. Hemo-concentration (hematocrit ≥ 20% of initial value) is one of the WHO criteria to diagnose DHF. Only few study reported no such association [8].

Similar to many studies, platelet ≤ 100,000/μL increased the risk of severity [10, 17, 28]. Platelet decreased rapidly before patients enter the state of shock. WHO also used platelets to categorize dengue infection into DHF grade I-IV [1]. Low platelet was explained by bone marrow suppression and immune-response induced platelet destruction by liver and spleen [5, 33, 36].

Some study concluded that white cell count > 5,000/μL is a prognostic factor for dengue severity [6, 15] while others found leucopenia [8, 12]. Normoleukocytosis or mild leukocytosis may be found in early dengue infection. When body temperature declines, most patients experienced leucopenia from bone marrow suppression [33]. Stress in accompanied with shock may somehow cause leukocytosis [6].

Biochemical

Elevated liver enzymes (SGOT and SGPT) are known as prognostic factors for DSS [15, 37]. When liver cells are infected, SGOT level is higher than SGPT particularly in severe cases [36]. The averaged SGOT and SGPT are higher in DHF than in DF [2]. Prolonged PTT and prolonged PT are prognostic factors for DHF and DSS [16, 17]. However, the present study and one other study [11] did not find such association. Elevated liver enzymes, prolonged PT and prolonged PTT normally occur after shock [11], which is too late to be used as prognostic indicators. Furthermore, SGOT, SGPT, PT, PTT are not routinely investigated in many hospitals, limiting their use in prognostic indicators.

Significant clinical parameters associated with severity of dengue infection may be used further in the development of a prognostic score, to forecast disease severity in patients suspected of dengue infection. If feasible, this forecasting may help early case management and reduce the overall morbidity and mortality.

Retrospective nature of the data limited its completeness of all clinical parameters of interests. However, we believe that information not investigated nor recorded in routine practice, are of limited values in perspectives of forecasting or prediction. With our relatively large sample size and multiple imputation techniques used for missing parameters, we believe that our results are likely to be valid.

Conclusions

The severity of dengue infection is significantly associated with some routine clinical parameters. These parameters may be used to develop a future scoring system to predict and manage dengue infection severity early in the course of the illness.

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Financial Disclosures and Conflict of Interests

None declared.

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