

FACTORS ASSOCIATED WITH SEVERE DENGUE INFECTION IN ADULTS

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Abstract. Dengue infections cause morbidity and mortality in Thailand. In the present study we aimed to identify factors associated with severe dengue in Thailand in order to identify those who are at high risk and give them a more intensive clinical observation. We recruited all subjects with dengue infection who presented to the Hospital for Tropical Diseases, Bangkok, Thailand during July 2019-February 2020. Inclusion criteria for study subjects were those aged ≥ 15 years who were from a Southeast Asian countries and were diagnosed with dengue infection by a positive NS1 antigen test, ELISA to detect dengue virus (DENV) IgM antibodies or polymerase chain reaction (PCR) test to detect DENV RNA. Severe dengue infection was defined by the 2009 WHO criteria as having hypotension from leakage, severe bleeding or organ impairment. The subjects' clinical manifestation on admission and the hematological and biochemical test results were recorded. These data were compared using multiple logistic regression analysis between those with and without severe dengue infection. A total of 416 patients were included in the study; 50% were male. The median (interquartile range) age of study subjects was 27.5 (22.0 -37.8) years. Of these, 10.3% had severe dengue infection. There were no demographic data significantly different between those with and without severe dengue infection. Factors significantly associated with severe dengue infection were having abdominal pain (odds ratio (OR) = 2.11; 95% confidence interval (CI): 1.05-4.22; $p = 0.03$), having bleeding (OR = 2.15; 95%CI: 1.07-4.32; $p = 0.03$) and transaminitis (liver enzymes elevated >200 U/l) (OR = 2.45; 95%CI: 1.22-4.92; $p = 0.01$). In conclusion, the incidence of severe dengue infection among our study subjects was 10.3% and the factors significantly associated with it were abdominal pain, bleeding and transaminitis. Dengue patients presented with these factors need intensive clinical observation because severe dengue may occur in these patients.

Keywords: dengue infection, associated factors, severe dengue, adults

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INTRODUCTION

Dengue infections cause morbidity and mortality in some tropical and subtropical regions (Wilder-Smith and Schwartz, 2005). There are an estimated 96 million cases of dengue infection world-

wide per year; of which 66.8 million cases were recorded in Asia (Bhatt *et al*, 2013). There are an estimated 500,000 cases of severe dengue infection world-wide per year with an estimated 12,500 deaths (2.5% mortality rate) (WHO, 2017a). Dengue is endemic in Thailand (Phanitchat, 2019). In 2018, there were 85,849 reported cases of dengue infection in Thailand, giving an infection rate of 129.9 cases per 100,000 populations; in 2018 there were also 111 deaths due to dengue infection reported from Thailand (Department of Diseases Control, 2019). There are four serotypes of dengue-virus (DENV) (WHO, 2009). DENV is a member of the Flaviviridae family (CDC, 2013). Infection with one of the DENV serotypes produces lifelong immunity against that serotype and cross-protective immunity against the other serotypes for a short period (2-12 months) (Wichmann and Jelinek, 2004). The principle vector for DENV is the female *Aedes* mosquito, such as *Aedes aegypti* and *Aedes Albopictus* (Gubler, 2002). *Aedes* spp usually feed during the daytime and can bite several people during their search for a blood meal (Gibbons and Vaughn, 2002). *Ae. aegypti* and *Ae. albopictus* prefer to lay their eggs in artificial containers, such as jars, pots and tires (Wilder-Smith and Schwartz, 2005). Female *Ae. aegypti* feed mainly on human blood, breed close to human habitats and have an almost unnoticeable bite (Gibbons and Vaughn, 2002). In humans, dengue has a mean incubation period of 5-7 days (CDC, 2019). The viremic phase usually lasts 4-5 days but can last up to 12 days (Gibbons and Vaughn, 2002). The mosquito must take a blood meal from a dengue infected person during this period to become a potential vector (WHO, 2017b). Transovarian transmission of DENV can occasionally occur in

some *Aedes* spp (Wichmann and Jelinek, 2004). International travel facilitates the spread of DENV and can increase the incidence rate of dengue infections (Ito *et al*, 2007). European travelers most commonly contract dengue infections in Indonesia, South Asia and South East Asia (SEA) (Jelinek *et al*, 2002). One study estimated that 10-43.5% of all global dengue cases were contracted in Thailand (Polwiang, 2015). In 2009, the World Health Organization (WHO) published guidelines for the diagnosis and treatment of dengue infection with definitions of probable dengue, dengue with warning signs and severe dengue, with a focus on monitoring warning signs and organ damage caused by severe plasma leakage (WHO, 2009). During 2013, dengue infections caused 1.14 million disability-adjusted life years (DALYs) globally with an estimated economic burden of USD8.9 billion (Hung *et al*, 2018). Dengue is Thailand's most important arboviral infection and it is the most common single cause of pediatric hospitalizations (Gubler, 2002; Wichmann *et al*, 2004). The estimated cost per hospitalization for each non-fatal dengue case during 2010 was USD528 while the total per capita cost due to dengue in Thailand that year was USD3.55 (Kongsin *et al*, 2010). Despite this, only a small number of studies have investigated risk factors associated with severe dengue among adults in SEA. A study conducted in Thailand found severe dengue to be associated with the following risk factors: age < 40 years, persistent vomiting, elevated atypical lymphocytes and elevated serum lactate levels (Thanachartwet *et al*, 2015). A study from Vietnam reported age (>60 years) to be associated with severe dengue (Huy *et al*, 2019). To date, there are no largescale studies investigating severe dengue

associated risk factors in Thailand. In this study, we investigated the incidence and the risk factors associated with severe dengue in adults in Bangkok, Thailand.

MATERIALS AND METHODS

We conducted a prospective observational study among patients hospitalized due to symptomatic dengue at the Hospital for Tropical Diseases, Bangkok, Thailand. Inclusion criteria for the study subjects were: having a positive test for dengue (dengue NS1 antigen, dengue IgM antibodies or a positive polymerase chain reaction test for dengue), being aged ≥ 15 years, being able to communicate with investigators and willing to participate in the study. The only exclusion criterion was being a patient from a country outside SEA. Each subject gave written informed consent prior to participation in the study. This study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand (approval no. MUTM 2019-049-01). Each subject's information was gathered using a standardized case record form (CRF). The following demographic data were collected at enrollment: age, gender, body weight, height and clinical manifestations. The following laboratory results were recorded on admission: the white blood cell count, hematocrit, hemoglobin, percentages of neutrophils, lymphocytes, and atypical lymphocytes, creatinine, serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT). The symptoms of the study participants were monitored regularly and laboratory tests were routinely performed during their hospitalization. Routine laboratory tests included: complete blood counts,

serum creatinine, SGOT and SGPT. The following warning signs according to WHO 2009 criteria were observed in participants during hospitalization: abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy or restlessness, liver enlargement >2 cm or an increase in hematocrit concurrent with rapid decrease in platelet count. Severe dengue was diagnosed following WHO 2009 criteria: severe plasma leakage leading to shock or respiratory distress from fluid accumulation, severe bleeding or severe organ involvement resulting in an elevated liver enzyme <1000 U/l, impaired consciousness, acute kidney injury (AKI) or heart failure (WHO, 2009). All participants received standard supportive care for their dengue infection. Participant data were entered into Microsoft Excel. The minimum number of participants needed for the study was calculated using the following equation: $(n = Z^2_{1-\alpha/2} * p(1-p) / d^2)$, where n is the minimum sample size; Z is the reliability factor; α is the confidence level; p is the proportion of severe dengue patients and d is the margin of error. According to previous studies from SEA, p is approximately 18% (0.18) (Aung *et al*, 2013; Huy *et al*, 2019; Thanachartwet *et al*, 2015; Xu *et al*, 2018). Reliability factor (Z) at α of 99% confidence is 2.576 while the margin of error (d) was set to 5%. Applying the equations from above resulted in a minimum sample size of 394 dengue infected subjects. Statistical analysis was performed using the Statistical Product and Service Solutions (SPSS) software, version 18.0 (IBM, New York City, NY). Continuous data are presented as means with standard deviations for normally distributed data and as medians with interquartile ranges (IQR) for data

that were not normally distributed. Categorical data are presented as numbers with percentages. An independent sample t-test or a Mann-Whitney U-test were used to compare continuous parameters. A Pearson's chi-squared test was used to compare categorical data. Logistic regression analysis was used to identify risk factors associated with severe dengue. All parameters which significantly differed between subjects with and without severe dengue infection were classified as possibly associated with severe dengue and added to the univariate logistic regression model. All factors which generated a p -value ≤ 0.2 on the univariate model were then included in the multivariate analysis model. A p -value < 0.05 was considered statistically significant.

RESULTS

Demographic data

A total of 416 subjects were included in the study (Fig 1); 10.3% with severe dengue infection. Among all subjects in this study, 64.9% had warning signs and 35.1% did not have warning signs (Fig 2). Participants were from Thailand (85.1%), Myanmar (7.2%), Laos (3.1%), Cambodia (2.4%), Vietnam (1.9%) and Malaysia (0.2%). The median (IQR) age of study subjects was 27.5 (22.0-37.8) (range: 15-88) years. The male to female ratio was 1:1. The underlying comorbidities in study subjects were: hypertension (7.0%), dyslipidemia (3.4%) and type 2 diabetes mellitus (2.9%). The median (IQR) body mass index (BMI) of participants was 22. (19.8-25.8) kg/m^2 . The BMI was

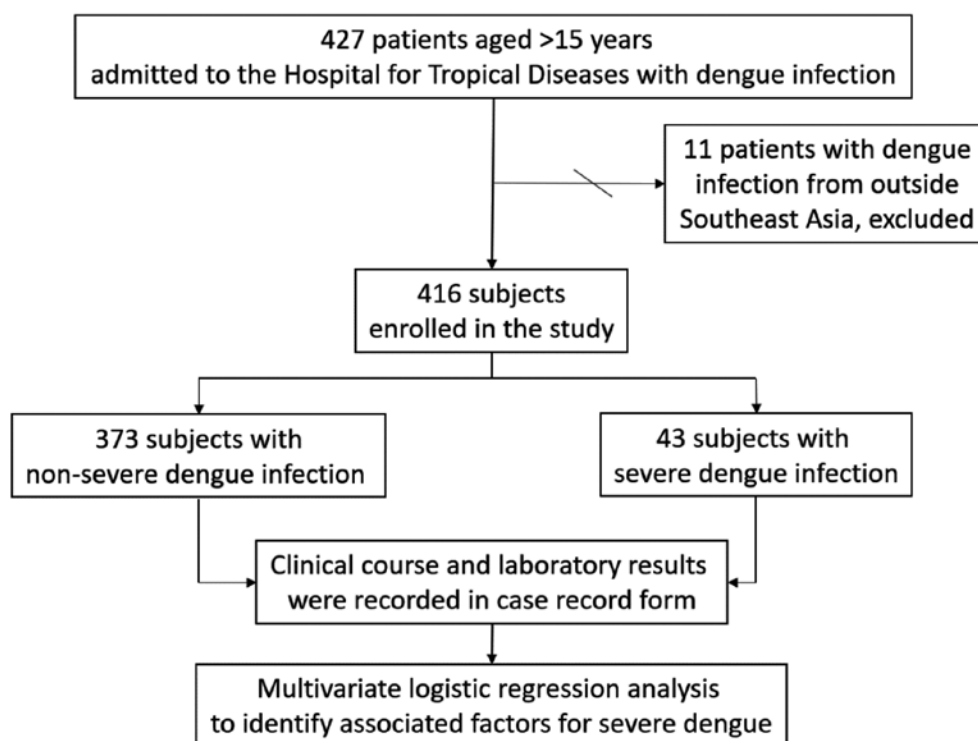


Fig 1-Flow chart of the study.

significantly higher ($p=0.007$) among those with (median BMI: 26.45 kg/m²; IQR: 20.55-28.44 kg/m²) compared to those without (median: 22.57 kg/m²; IQR: 19.77-25.80 kg/m²) severe dengue infection. BMI was the only parameter significantly different between those with and without severe dengue infection. (Table 1).

Signs and symptoms on admission

The most common signs and symptoms on admission were: myalgia (94%), headache (82.9%), periorbital pain (59.2%), abdominal pain (47.6%) vomiting (46.6%), bleeding (42.9%) and hepatomegaly (20.9%). The symptoms on admission significantly more common among those with than those without severe dengue infection were: abdominal pain (47.6% vs 26.1%, $p=0.003$), bleeding (42.9% vs 23.9%, $p=0.008$) and hepatomegaly (20.9% vs 7.2%, $p=0.002$) (Table 2).

Laboratory results on admission

The laboratory results significantly different between subjects with and without severe dengue infection were: a higher mean total white blood cell count (3200 cells/ μ l vs 3000 cells/ μ l; $p = 0.03$), a higher mean SGOT level (150 U/l vs 79.5 U/l; $p <0.001$) and a higher mean SGPT level (107 U/l vs 51.5 U/l; $p <0.001$) (Table 3).

Factors associated with severe dengue infection

On univariate analysis, factors associated with ($p<0.2$) severe dengue infection were: vomiting, abdominal pain, bleeding, hepatomegaly and transaminitis. On multivariable logistic regression analysis, factors significantly associated ($p<0.05$) with severe dengue infection were: abdominal pain (adjusted odds ratio (adjusted OR) = 2.11; 95% confidence interval (CI): 1.05-4.22; $p =$

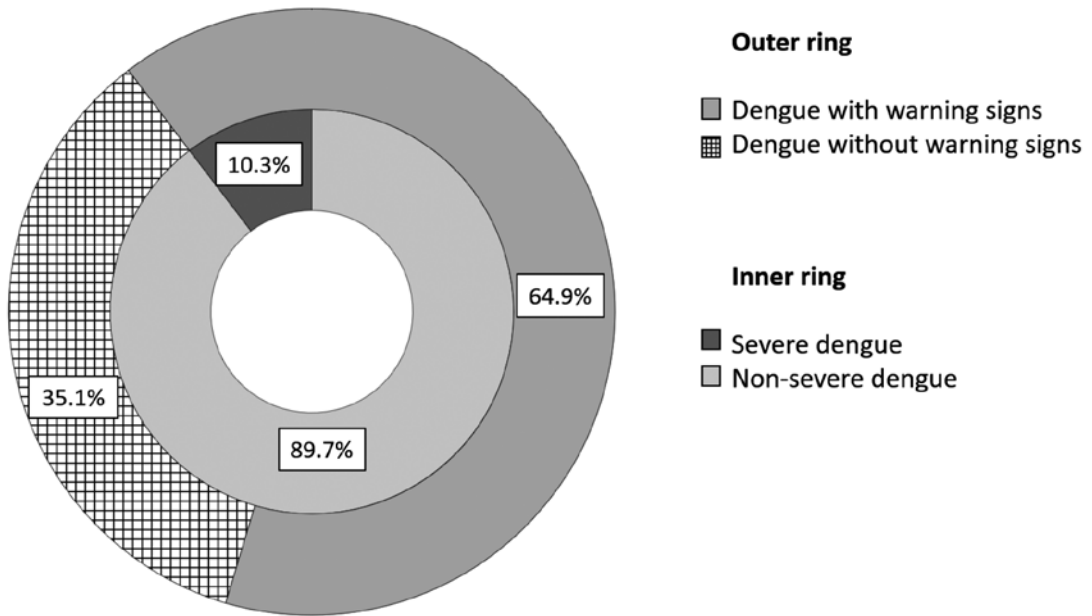


Fig 2-Ring chart classifying study subjects.

Table 1
Characteristics of study subjects classified by severity of dengue infection.

Characteristics	Total	Non-severe dengue infection	Severe dengue infection	p-value
	(n = 416)	(n = 373)	(n = 43)	
Male gender, n (%)	208 (50)	186 (49.9)	22 (51.2)	0.872
Median (IQR) age in years	27 (22-37)	27 (22-37)	29 (24-46)	0.114
Median (IQR) body mass index in kg/m ²	22.9 (19.9-26.2)	22.6 (19.8-25.8)	26.5 (20.6-28.4)	0.007*
History of underlying disease, n (%)				
Type 2 diabetes	12 (2.9)	11 (2.9)	1 (2.3)	0.817
Hypertension	29 (7.0)	26 (7.0)	3 (7.0)	0.999
Dyslipidemia	14 (3.4)	12 (3.2)	2 (4.7)	0.621
Mean±SD heart rate in beats/minute	83±15	83±14	86±18	0.192
Mean±SD respiratory rate in breaths/minute	20±2	20±2	21±2	0.127
Mean±SD arterial pressure in mmHg	85±10	84±10	86±9	0.255
Male gender, n (%)	208 (50)	186 (49.9)	22 (51.2)	0.872

*statistically significant; SD: standard deviation, IQR: interquartile range; kg/m²: kilogram per square meter.

0.03), bleeding (adjusted OR = 2.15; 95% CI: 1.07-4.32; $p = 0.03$), and high SGOT/SGPT levels (adjusted OR = 2.45; 95% CI: 1.22-4.92; $p = 0.01$) (Table 4).

DISCUSSION

In our study, 10.3% of subjects had severe dengue infection and 54.6% of subjects had warning signs with their dengue infection. The proportion of severe dengue cases in our study is similar to those reported in previous studies from Thailand (14%) (Thanachartwet *et al*, 2015), Myanmar (11%) (Kyaw *et al*, 2015) and Vietnam (11%) (Huy *et al*, 2019). In our study, most of the subjects were aged 20-

40 years. A previous study from Thailand reported 81.6% of subjects were aged ≤ 40 years (Thanachartwet *et al*, 2015). A study from Singapore reported the median age of study subjects with dengue infection was 39 years (Xu *et al*, 2018). A study from Vietnam reported 65.3% of study subjects were aged 21-40 years (Huy *et al*, 2019).

In our study, the most common symptoms among subjects with severe dengue infection were: myalgia, headache and periorbital pain. Two studies from Thailand reported the most common symptoms among study subjects with severe dengue infection were: headache, vomiting, myalgia and abdominal pain

Table 2
Symptoms and signs of study subjects on admission classified by severity of dengue infection.

Symptoms and signs on admission	Total	Non-severe dengue infection	Severe dengue infection	<i>p</i> -value
	(<i>n</i> = 416) number (%)	(<i>n</i> = 373) number (%)	(<i>n</i> = 43) number (%)	
Headache	343 (82.9)	306 (82.3)	37 (88.1)	0.341
Periorbital pain	245 (59.2)	220 (59.1)	25 (59.5)	0.962
Dyspnea	167 (40.3)	150 (40.3)	17 (40.5)	0.985
Myalgia	389 (94.0)	349 (93.8)	40 (95.2)	0.714
History of rash	97 (23.4)	88 (23.7)	9 (21.4)	0.747
Vomiting	193 (46.6)	169 (45.4)	24 (57.1)	0.149
Abdominal pain	117 (28.3)	97 (26.1)	20 (47.6)	0.003*
Diarrhea	173 (41.8)	152 (40.9)	21 (50.0)	0.255
Bleeding	107 (25.8)	89 (23.9)	18 (42.9)	0.008*
Hepatomegaly	36 (8.7)	27 (7.2)	9 (20.9)	0.002*
Splenomegaly	1 (0.2)	1 (0.3)	0 (0)	N/A
Skin rash	48 (11.5)	43 (11.5)	5 (11.6)	0.985

*statistically significant by Pearson Chi-square test; N/A: not applicable.

Table 3
Laboratory results of study subjects on admission by severity of dengue infection.

Laboratory results on admission	Total	Non-severe dengue infection	Severe dengue infection	<i>p</i> -value
	(<i>n</i> = 416)	(<i>n</i> = 373)	(<i>n</i> = 43)	
Median (IQR) white blood cell count; cells/ μ l	3025 (2300-4100)	3000 (2245-4000)	3200 (2600-4840)	0.03*
Mean \pm SD hemoglobin level in g/dl	14.3 \pm 1.7	14.3 \pm 1.7	14.1 \pm 1.8	0.517
Mean \pm SD hematocrit in percent	43.2 \pm 4.7	43.2 \pm 4.7	43.3 \pm 5.0	0.848
Mean \pm SD percentage of neutrophils	51.7 \pm 16.6	51.3 \pm 16.6	55.5 \pm 16.0	0.109
Mean \pm SD percentage of lymphocytes	27.4 \pm 11.1	27.8 \pm 11.05	24.5 \pm 11.4	0.071
Median (IQR) percentage of atypical lymphocytes	7.0 (2.0-15.0)	7.0 (2.0-16.0)	6.0 (2.0-14.0)	0.066

Table 3 (Continued)

Laboratory results on admission	Total	Non-severe dengue infection	Severe dengue infection	p-value
	(n = 416)	(n = 373)	(n = 43)	
Median (IQR) creatinine level in mg/dl	0.88 (0.26-7.97)	0.86 (0.70-1.04)	0.97 (0.75-1.09)	0.226
Median (IQR) SGOT level in U/l	88 (50.5-197)	79.5 (48-170.5)	150 (88-543.5)	< 0.001*
Median (IQR) SGPT level in U/l	55 (30-115)	51.5 (28-104.5)	107 (56-441)	< 0.001*

*statistically significant by Mann-Whitney test; SGOT: serum glutamic-oxaloacetic transaminase; SGPT: serum glutamic-pyruvic transaminase; SD: standard deviation; IQR: interquartile range; μ l: microliter; g/dl: gram per deciliter; mg/dl: milligram per deciliter; U/l: units per liter.

Table 4
Logistic regression analysis of factors associated with severe dengue infection.

Independent variables	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
Vomiting	1.60	0.84-3.05	0.152	1.07	0.53-2.18	0.846
Abdominal pain	2.58	1.35-4.93	0.004	2.11	1.05-4.22	0.036*
Bleeding	2.39	1.24-4.60	0.009	2.15	1.07-4.32	0.032*
Hepatomegaly	3.39	1.48-7.80	0.004	2.44	0.98-6.11	0.056
Transaminitis (SGOT or SGPT >200 U/l)	3.47	1.81-6.66	< 0.001	2.45	1.22-4.92	0.011*
Body mass index ≥ 30 kg/m ²	1.57	0.62-3.97	0.345	-	-	-

*statistically significant; SGOT: serum glutamic-oxaloacetic transaminase; SGPT: serum glutamic-pyruvic transaminase; OR: odds ratio; CI: confident interval; kg/m²: kilogram per square meter; U/l: units per liter.

(Aung *et al*, 2013; Tempraserttrudee *et al*, 2018). Another study from Thailand reported the most common signs and symptoms among study subjects with severe dengue infection on admission were: myalgia, headache and hepatomegaly (Thanachartwet *et al*, 2015).

In this study, factors significantly associated with severe dengue were: abdominal pain, bleeding, and elevated

SGOT/SGPT levels. A previous study from Malaysia reported the most common signs and symptoms associated with severe dengue infection were: abdominal pain, vomiting, bleeding and hepatomegaly (Ahmad *et al*, 2018). One study from Thailand reported the factors significantly associated with severe dengue infection were: age >40 years, vomiting, an absolute atypical lymphocyte count of >300

cells/ μ l and a serum lactate level ≥ 2.00 mmol/l (Thanachartwet *et al*, 2015). One study from Thailand reported the factors associated with severe dengue infection were: age, hepatomegaly, a low neutrophil count and an SGOT level >120 U/l (Temprasertudee *et al*, 2018). Another study from Thailand reported the factors associated with severe dengue infection were: female gender and mean arterial pressure <80 mmHg (Aung *et al*, 2013). A study from Malaysia reported the factors significantly associated with mortality in dengue infection were: bleeding and elevated SGOT/SGPT tests at the time of diagnosis (Md-Sani *et al*, 2018).

Limitations of our study were: the laboratory tests were dependent on the attending physician and the study was conducted at only one institution. However, our sample size was calculated to allow sufficient statistical power to determine factors associated with severe dengue infection.

Abdominal pain, bleeding and transaminitis on admission are factors associated with severe dengue in adults. Further studies are needed to determine whether these factors can detect patients who will progress to severe dengue infection or not. Further studies are also needed to determine if these factors can be used to guide management of severe dengue infection and better outcomes.

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