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Factors associated with severe dengue in Savannakhet Province, Lao People's Democratic Republic

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ABSTRACT

This study aimed to describe the socio-demographic and clinical characteristics of dengue inpatients at a provincial hospital, and to identify factors associated with severe dengue. This is a retrospective study involving 402 dengue patients admitted to the Savannakhet Provincial Hospital, Lao People's Democratic Republic (Lao PDR), between January 2018 and April 2019. Socio-demographic factors, clinical signs and laboratory data on admission, final diagnosis, use of health care services before admission, admission date, and hospitalization period were collected from patient records. The number of dengue inpatients was higher in the rainy season than in the dry season. Of the 402 patients, 205 patients (51.0%) were finally diagnosed with severe dengue. Children aged <15 years had more symptoms, higher proportion of severe dengue (69.8% vs. 35.9%), and longer hospitalization (3.5 days vs. 3.0 days) than adults aged ≥15 years. In multivariable analyses, factors associated with severe dengue were nausea on admission (adjusted odds ratio=3.57, 95% CI=1.05–12.09, *P*=0.04) in children and persistent vomiting on admission (adjusted odds ratio=3.82, 95% CI=1.23–11.92, *P*=0.02) in adults. In adults, the creatinine level on admission was significantly higher in patients with a final diagnosis of severe dengue compared to the others. The proportion of severe dengue in our study was higher than that in other countries. Nausea and persistent vomiting on admission were suggested to be predictive factors for severe dengue. To reduce the incidence of severe dengue in Lao PDR, improvements in access to health care, referral system, and training of health care workers are needed.

Keywords: children, Lao PDR, nausea, persistent vomiting, severe dengue

Abbreviations:
AKI: acute kidney injury
ALT: alanine aminotransferase
ARDS: acute respiratory distress syndrome
AST: aspartate aminotransferase
CFR: case fatality rate
CRT: capillary refill time

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Lao PDR: Lao People's Democratic Republic
NCLE: National Central Laboratory and Epidemiology
NS1: nonstructural protein 1
TT: tourniquet test
WHO: World Health Organization

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INTRODUCTION

Dengue is a mosquito-borne infectious disease. It is one of the global public health issues given its high incidence in more than 100 countries. The incidence of dengue is very high in the tropical and sub-tropical countries, especially those in the Western Pacific region and South East Asia.[1-3] Globally, the annual number of new dengue cases is 50–100 million, and approximately 500,000 people with severe dengue are hospitalized every year with a case fatality rate (CFR) of 2.5%.[1,2] Globally, more than two billion people are at risk of dengue infection, mostly in Asian countries including Lao People Democratic Republic (Lao PDR).[1,2,4] The annual number of dengue patients hospitalized from 2001 to 2010 was, on average, 816,000 patients, with 5,900 deaths in South East Asia and 18,000 cases and 41 deaths estimated in Lao PDR.[5] In Thailand, the incidence of dengue infections increased over the last 50 years, from 189 cases per 100,000 population in 1958 to 218 cases per 100,000 population in 2011.[6] In June 2019, the World Health Organization (WHO) reported that the number of dengue cases was much higher than that in the same period in the previous year in Asian countries, such as Lao PDR, Cambodia, Vietnam, the Philippines, Malaysia, and Bangladesh.[7]

There are four serotypes of the dengue virus, namely DENV-1, DENV-2, DENV-3, and DENV-4. All serotypes cause similar symptoms, although approximately 35% of the genome in each serotype is different.[8] High fever is the most common symptom, followed by pain, gastro-intestinal symptoms, skin reactions, bleeding, fluid accumulation, and neurological symptoms.[9-11] There are three phases of dengue infection: febrile phase, 2–7 days; critical phase, 24–48 hours; and recovery phase, 48–72 hours.[9,10,12] A person infected with the dengue virus develops cross-protection against other serotypes but only for 1–3 years.[13] Secondary dengue infection with another serotype and multiple infections are considered a severe condition.[2,11] The WHO classification of dengue severity defines three categories: dengue without warning signs, dengue with warning signs, and severe dengue.[9] The warning signs of dengue are persistent vomiting, mucosal bleeding, fluid accumulation, abdominal pain or tenderness, lethargy/restlessness, liver enlargement >2 cm, and hematocrit elevation >20% concurrent with a rapid decrease in platelet count to ≤100,000/μL. Severe dengue is characterized by severe plasma leakage, severe bleeding, and severe organ impairment.[2,9,14]

In Lao PDR, dengue is a major public health issue.[15] There have been dengue epidemics in the past: 17,500 cases in 1998 and 2003, 22,890 cases including 46 deaths in 2010, and 44,171 cases including 95 deaths in 2013.[16] The Ministry of Health collaborated with WHO to develop the treatment guidelines for dengue patients, provide clinical training at hospitals, and establish laboratory and surveillance systems in five provinces (Champasack, Savannakhet, Laungphrabang, Laungnamtha, and Oudomxay).[4] Savannakhet Province has the second highest number of dengue cases in the country. The CFR increased from 0.18% (nine deaths out of 4,959 cases) in 2013 to 0.98% in the 2018 outbreak according to the report of the National Central Laboratory and Epidemiology (NCLE).[16] To reduce the mortality due to dengue, it is important to recognize patients of dengue with warning signs and manage patients of severe dengue.[9] This study aimed

to describe the socio-demographic and clinical characteristics of dengue inpatients at a provincial hospital, and to identify factors associated with severe dengue.

MATERIALS AND METHODS

Study design and participants

This was a retrospective study involving dengue patients who were admitted to the intensive care unit, internal medicine ward, and pediatric ward of Savannakhet Provincial Hospital between January 2018 and April 2019. Patients were diagnosed with dengue by detection of nonstructural protein 1 (NS1) antigen on reverse transcription polymerase chain reaction or immunoglobulin M (IgM) and IgG antibodies on enzyme linked immunosorbent assay. The examinations were performed at the Savannakhet Provincial Hospital and/or NCLE in Vientiane Capital. Patients whose medical records were unavailable were excluded. In total, 402 dengue patients were included in this study.

Definition of clinical symptoms and signs of dengue

The tourniquet test (TT) is used to determine capillary breakability. A patient's arm was fastened by a blood pressure cuff with the cuff inflated to midway between systolic and diastolic blood pressure for five minutes. When the number of petechiae in a 2.5 cm^2 area in the distal part of the cuff was more than 15, the test result was considered to be positive.[9,10,17] WHO recommends using the TT as a clinical diagnostic tool for dengue and repeating the test to increase the sensitivity.

Persistent vomiting was defined as a patient vomiting more than two times within 24 hours. Mucosal bleeding included bleeding in the gums, conjunctiva, skin ecchymosis or purpura. Fluid accumulation included namely pleural effusion, pulmonary edema, and ascites, was diagnosed using chest radiography and abdominal ultrasonography. Liver enlargement was measured using abdominal examination (palpation and percussion) and abdominal ultrasonography.[2,9,10,14]

Diagnosis of severe dengue

Patients were diagnosed with severe dengue when they met at least one of three criteria: severe plasma leakage, severe bleeding, and severe organ impairment. Severe plasma leakage was diagnosed when a patient had plasma leakage with symptoms of shock, such as weak and rapid pulse, cold extremities, capillary refill time (CRT) greater than 2 seconds, narrow pulse pressure (≤20 mmHg) with normal or slightly high systolic blood pressure (eg, 110/95 mmHg) in compensating shock, lower blood pressure than normal in hypotensive shock, or prolonged shock. CRT is measured by the time it takes for color to return to an external capillary bed after pressure is applied to cause blanching, and the CRT is usually 2 seconds or less in healthy people.[9,10,18] Severe plasma leakage is the main cause of dengue shock syndrome, which is a form of hypovolemic shock, and acute respiratory distress syndrome (ARDS).[2,9,12]

Severe bleeding was diagnosed with clinical symptoms, such as gastrointestinal bleeding (blood in vomit, melena) or severe vaginal bleeding, with decreasing levels of hematocrit and hemoglobin, and shock status without recovery after crystalloid resuscitation.[4,9,10]

Severe organ impairment occurs when a patient is in a prolonged shock status.[9,12] Severe organ impairment was diagnosed when a patient met at least one of the criteria of acute kidney injury (AKI), ARDS, acute liver failure with encephalopathy or encephalitis, and cardiomyopathy.[9] AKI can lead to pulmonary edema and respiratory distress. AKI was diagnosed when the urine output was less than 0.5 mL/kg/h with a rise in the creatinine level ≥2 mg/dL. To confirm the

diagnosis of ARDS, pulmonary edema and respiratory distress were identified by wheezing or crepitation on pulmonary examination, besides the respiratory rate measurements and chest radiography findings.[9,18] Although the criteria were not clearly set, acute liver failure was diagnosed by an increase in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels of ≥1,000U/L with jaundice symptom, increase in total bilirubin with coagulopathy, and hepatic encephalopathy with no evidence of prior liver disease. The symptoms of hepatic encephalopathy included movement disorder, change in mood or personality, and, in the advanced stage, coma. Cardiomyopathy was diagnosis using electrocardiogram and echocardiography.[9,12,19]

Data collection

The following data were collected from the medical record books of the hospital: (1) dates of admission and discharge, (2) socio-demographic data (age, sex, occupation, nationality, ethnic group, and religion), (3) medical history (congenital disease, pregnancy, obesity, diabetic, hypertension, renal failure, liver diseases, chronic hemolytic diseases, and peptic ulcer), (4) usage of a health facility before admission to the hospital (pharmacies, private clinics, health centers, district hospitals, and the provincial hospital), (5) clinical symptoms and signs on admission, (6) final diagnosis of dengue (dengue without warning signs, dengue with warning signs, severe dengue), and (7) laboratory data on admission (hemoglobin, hematocrit, platelet, creatinine, glucose, sodium, ALT, and AST levels). Clinical symptoms and signs included general symptoms (fever, TT, or skin rash), pain and ache (headache, myalgia, general body ache, or arthralgia), gastrointestinal symptoms (nausea, anorexia, severe abdominal pain, vomiting, persistent vomiting, or liver enlargement), plasma leakage (ascites or pleural effusion), cardiovascular signs (CRT, weak and rapid pulse, or cold extremities), bleeding (petechiae, mucosal bleeding, severe vaginal bleeding, melena, or blood in vomit), and neurological symptoms (lethargy/restlessness, dizziness, or convulsion).

Statistical analysis

Final diagnoses were categorized into non-severe dengue and severe dengue. Non-severe dengue included dengue with or without warning signs. A chi-square test was performed to examine a relationship between two categorical variables, but Fisher's exact test was used when more than 20% of cells had expected frequencies <5. A *t*-test was performed to compare the means of two groups. A logistic regression model was used to determine the odds ratio (OR) and 95% confidence interval (CI). In the logistic regression analyses on severe dengue, age, sex, occupation, usage of health facilities before admission, and clinical symptoms and signs on admission were used as independent variables. In adults, 15 clinical signs on admission were used: fever, TT, skin rash, headache, myalgia, general body ache, arthralgia, nausea, anorexia, severe abdominal pain, vomiting, persistent vomiting, pleural effusions, mucosal bleeding and dizziness. In children, the same signs, except dizziness, were included because young children might find it difficult to explain dizziness. Multivariable logistic regression analyses on the final diagnosis of severe dengue were performed in the forced-entry method, and the forward and backward stepwise selection. The criteria for variable selection were $P < 0.05$ for adding variables, and $P > 0.1$ for removing variables. A p-value <0.05 was deemed to be statistically significant. Data were analyzed using IBM SPSS statistic software version 26 (IBM SPPS Inc).

Ethical considerations

The requirement for written informed consent was waived owing to the retrospective nature of the study, and ethical approval for this study was obtained from the National Ethics Committee for Health Research, Ministry of Health, on August 9, 2019 (issue number 089/NECHR).

RESULTS

Fig. 1 shows that the number of dengue inpatients at the Savannakhet Provincial Hospital was higher in the rainy season (from July to October) than in the dry season (from November to June). The highest number of admissions per week was 36 during weeks 29 and 33.

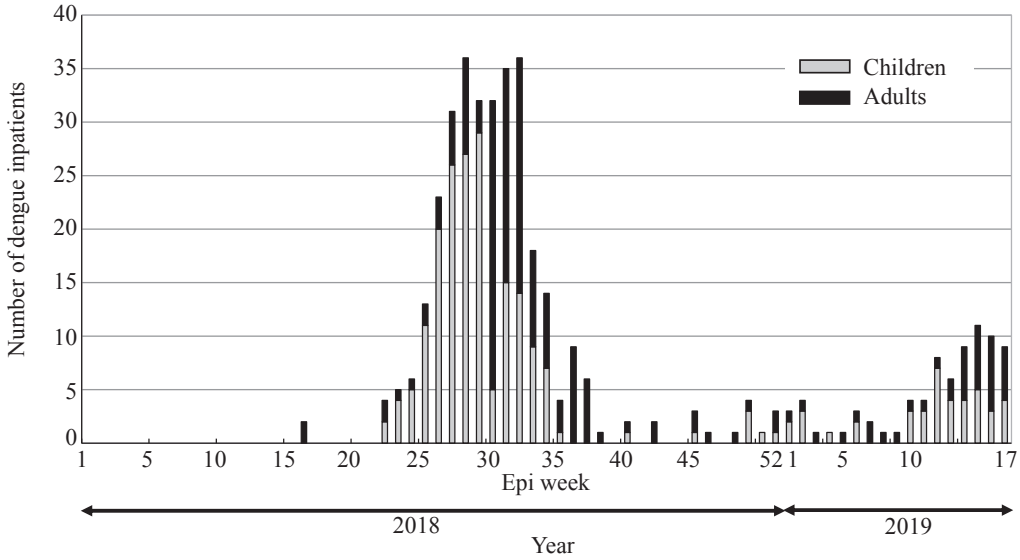

Fig. 1 Distribution of dengue inpatients at Savannakhet Provincial Hospital from January 2018 to April 2019

The black (adults) and grey (children) bars show the number of dengue patients who were admitted to the provincial hospital in each epi week.

A total of 402 (196 male and 206 female) dengue patients were included in this study (Table 1). There were 179 children aged 1–14 years and 223 adults aged ≥15 years. Most patients were Lao-lum (94.0%) and Buddhist (93.8%). The underlying conditions were peptic ulcers in nine patients, hypertension in seven patients, obesity in six patients, pregnancy in three patients, and renal failure in one patient.

Table 2 shows a comparison of characteristics and clinical factors between children and adults. The children's group had significantly more female patients (57.0%) than the adult group (46.6%, $P = 0.039$). Children used health facilities before admission more often (84.9%) than adults (47.9%, $P < 0.001$). Of the 107 adult patients who used health facilities, most patients visited district hospitals or the provincial hospital (n = 100). The major symptoms on admission were pain and ache, such as headache (96.8%), myalgia (92.5%), general body ache (88.6%), and arthralgia (74.1%). The common gastrointestinal symptoms were nausea (68.4%), anorexia (59.5%), severe abdominal pain (57.2%), vomiting (48.5%), dizziness (42.3%), and mucosal bleeding (28.9%). The TT result was positive in 85.0% of the patients. Ascites and convulsion were observed only in four patients and one patient, respectively. There were significant differences in many clinical signs on admission between children and adults patients, and children had more symptoms than adults: general body ache (95.0% vs. 83.4%, $P < 0.001$), arthralgia (82.7% vs.

67.3%, P <0.001), nausea (88.3% vs. 52.5%, P <0.001), anorexia (84.9% vs. 39.0%, P <0.001), severe abdominal pain (72.1% vs. 45.3%, P <0.001), vomiting (51.8% vs. 48.2%, P = 0.004), persistent vomiting (32.4% vs. 10.3%, P <0.001), cold extremities (28.5% vs. 9.4%, P <0.001), and lethargy/restlessness (10.0% vs. 2.7%, P = 0.002). The objective signs that children showed more than adults were weak pulse (17.3% vs. 5.4%, P <0.001), liver enlargement (21.8% vs. 0.4%, P <0.001), and CRT >2s (21.2% vs. 11.2%, P = 0.006). Severe vaginal bleeding was found in nine of 104 female adult patients (6.4%).

The final diagnosis was severe dengue in 205 patients (51.0%), and the incidence of severe dengue in children (69.8%) was significantly higher than that in adults (35.9%) (P <0.001, Table 2). The mean hospitalization duration was 3.2 days (standard deviation 1.3), and it was significantly longer in children than adults (3.5 days vs 3.0 days, P = 0.006). There was no case of death in our study population.

Table 1 Socio-demographic characteristics of patients according to children and adults

Variables	Total (N=402)		Children (N=179)		Adults (N=223)	
	n	(%)	n	(%)	n	(%)
Age (years)						
1–4	11	(2.7)	11	(6.1)	-	-
5–14	168	(41.8)	168	(93.9)	-	-
15–24	125	(31.1)	-	-	125	(56.1)
25–44	85	(21.2)	-	-	85	(38.1)
45–82	13	(3.2)	-	-	13	(5.8)
Sex						
Male	196	(48.8)	77	(43.0)	119	(53.4)
Female	206	(51.2)	102	(57.0)	104	(46.6)
Occupation						
None	80	(19.9)	52	(29.0)	28	(12.6)
Student	193	(48.0)	126	(70.4)	67	(30.0)
Officer	16	(4.0)	-	-	16	(7.2)
Farmer/self-employed	113	(28.1)	1	(0.6)	112	(50.2)
Nationality						
Lao	398	(99.0)	178	(99.4)	220	(98.7)
Other[a]	4	(1.0)	1	(0.6)	3	(1.3)
Ethnic group						
Lao-lum	378	(94.0)	158	(88.3)	220	(98.7)
Other[b]	24	(6.0)	21	(11.7)	3	(1.3)
Religion						
Buddhist	377	(93.8)	158	(88.3)	219	(98.2)
Other[c]	25	(6.2)	21	(11.7)	4	(1.8)

[a]Other includes Vietnamese and Chinese.
[b]Other includes Khemu and Hmong.
[c]Other includes Ghost and Christian.

Table 2 Comparison of clinical factors between children and adults

Variables	Total (N=402)		Children (N=179)		Adults (N=223)		*P*-value[a]
	n	(%)	n	(%)	n	(%)	
Sex							
Male	196	(48.8)	77	(43.0)	119	(53.4)	0.039
Female	206	(51.2)	102	(57.0)	104	(46.6)	
Use of health facilities before admission							
No	143	(35.6)	27	(15.1)	116	(52.0)	<0.001
Pharmacy	26	(6.5)	24	(13.4)	2	(0.9)	
Hospital[b]	213	(53.0)	113	(63.1)	100	(44.8)	
Other[c]	20	(5.0)	15	(8.4)	5	(2.2)	
Clinical symptoms and signs on admission							
General							
Fever	89	(22.1)	39	(21.8)	50	(22.4)	0.879
Tourniquet test (+)	342	(85.0)	158	(88.3)	184	(82.5)	0.107
Skin rash	32	(8.0)	17	(9.5)	15	(6.7)	0.308
Pain and ache							
Headache	389	(96.8)	173	(96.6)	216	(96.9)	0.905
Myalgia	372	(92.5)	167	(93.3)	205	(91.9)	0.604
General body ache	356	(88.6)	170	(95.0)	186	(83.4)	<0.001
Arthralgia	298	(74.1)	148	(82.7)	150	(67.3)	<0.001
Gastro intestinal system							
Nausea	275	(68.4)	158	(88.3)	117	(52.5)	<0.001
Anorexia	239	(59.5)	152	(84.9)	87	(39.0)	<0.001
Severe abdominal pain	230	(57.2)	129	(72.1)	101	(45.3)	<0.001
Vomiting	195	(48.5)	101	(51.8)	94	(48.2)	0.004
Persistent vomiting	81	(20.1)	58	(32.4)	23	(10.3)	<0.001
Liver enlargement	40	(10.0)	39	(21.8)	1	(0.4)	<0.001
Plasma leakage							
Pleural effusions	11	(2.7)	3	(1.7)	8	(3.6)	0.359
Ascites	4	(1.0)	1	(0.6)	3	(1.3)	0.632
Cardiovascular system							
CRT >2s	63	(15.7)	38	(21.2)	25	(11.2)	0.006
Weak pulse	43	(10.7)	31	(17.3)	12	(5.4)	<0.001
Cold extremities	72	(17.9)	51	(28.5)	21	(9.4)	<0.001
Bleeding							
Petechia	7	(1.7)	3	(6.0)	4	(20.0)	1.000
Mucosal bleeding	116	(28.9)	58	(32.4)	58	(26.0)	0.160
Sever vaginal bleeding	9	(2.2)	0	(0.0)	9	(4.0)	-
Melena	14	(3.5)	8	(4.5)	6	(2.7)	0.334
Blood in vomit	7	(1.7)	5	(2.8)	2	(0.9)	0.250
Central nervous system							
Lethargy/restless	24	(6.0)	18	(10.0)	6	(2.7)	0.002
Dizziness	170	(42.3)	101	(56.4)	69	(40.6)	<0.001
Convulsion	1	(0.2)	0	(0.0)	1	(0.4)	1.000
Final diagnosis							
Non-severe dengue	197	(49.0)	54	(30.2)	143	(64.1)	<0.001
Severe dengue	205	(51.0)	125	(69.8)	80	(35.9)	
Hospitalization period (days)							
Mean (SD)	3.2	(1.3)	3.5	(1.2)	3.0	(1.3)	0.006

CRT >2s, capillary refill times more than 2 seconds.
SD: standard deviation
[a]A *t*-test was used for comparison of the mean of hospitalization period. A chi-square test and Fisher's exact test were used for the other variables.
[b]Hospital includes district hospitals and the provincial hospital.
[c]Other includes health centers and private clinics.

Table 3 Association between socio-demographic factors and clinical signs on admission with severe dengue in children

Variables	Non-severe dengue (N=54)	Severe dengue (N=125)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]	*P*-value
	n (%)	n (%)			
Age group (years)					
0–4	1 (9.1)	10 (90.9)	1 (Reference)	1 (Reference)	0.08
5–14	53 (31.5)	115 (68.5)	0.22 (0.03–1.74)	0.10 (0.01–1.32)	
Sex					
Male	26 (33.8)	51 (66.2)	1 (Reference)	1 (Reference)	0.43
Female	28 (27.5)	74 (72.5)	1.35 (0.71–2.56)	1.34 (0.65–2.78)	
Occupation					
Student	39 (31.0)	87 (69.0)	1 (Reference)	1 (Reference)	0.52
None	15 (28.3)	38 (71.7)	1.15 (0.10–13.06)	0.75 (0.31–1.81)	
Use of health facilities before admission					
No	7 (25.9)	20 (74.1)	1 (Reference)	1 (Reference)	
Pharmacy	9 (37.5)	15 (62.5)	0.58 (0.18–1.93)	0.39 (0.83–1.81)	0.23
Hospital[b]	35 (31.0)	78 (69.0)	0.78 (0.30–2.01)	0.60 (0.17–2.16)	0.43
Other[c]	3 (20.0)	12 (80.0)	1.40 (0.30–6.47)	1.33 (0.21–8.25)	0.76
Clinical symptoms and signs on admission					
Fever					
No	43 (30.7)	97 (69.3)	1 (Reference)	1 (Reference)	0.66
Yes	11 (28.2)	28 (71.8)	1.13 (0.52–2.47)	1.26 (0.45–3.50)	
Tourniquet test					
(–)	5 (23.8)	16 (76.2)	1 (Reference)	1 (Reference)	0.27
(+)	49 (31.0)	109 (69.0)	0.70 (0.24–2.01)	0.50 (0.15–1.70)	
Skin rash					
No	49 (30.2)	113 (69.8)	1 (Reference)	1 (Reference)	0.48
Yes	5 (29.4)	12 (70.6)	1.04 (0.35–3.11)	0.62 (0.17–2.31)	
Headache					
No	3 (50.0)	3 (50.0)	1 (Reference)	1 (Reference)	0.62
Yes	51 (29.5)	122 (70.5)	2.39 (0.47–12.25)	1.69 (0.21–13.46)	
Myalgia					
No	4 (33.3)	8 (66.7)	1 (Reference)	1 (Reference)	0.78
Yes	50 (29.9)	117 (70.1)	1.17 (0.34–4.06)	1.29 (0.21–8.02)	
General body ache					
No	2 (22.2)	7 (77.8)	1 (Reference)	1 (Reference)	0.47
Yes	52 (30.6)	118 (69.4)	0.65 (0.13–3.23)	0.48 (0.07–3.56)	
Arthralgia					
No	12 (38.7)	19 (61.3)	1 (Reference)	1 (Reference)	0.19
Yes	42 (28.4)	106 (71.6)	1.59 (0.71–3.57)	2.10 (0.68–6.46)	
Nausea					
No	11 (52.7)	10 (47.6)	1 (Reference)	1 (Reference)	0.04
Yes	43 (27.2)	115 (72.8)	2.94 (1.17–7.42)*	3.57 (1.05–12.09)	
Anorexia					
No	9 (33.3)	18 (66.7)	1 (Reference)	1 (Reference)	0.89
Yes	45 (29.6)	107 (70.4)	1.19 (0.50–2.85)	0.91 (0.25–3.38)	
Severe abdominal pain					
No	16 (32.0)	34 (68.0)	1 (Reference)	1 (Reference)	0.42
Yes	38 (29.5)	91 (70.5)	1.13 (0.56–2.28)	0.69 (0.27–1.72)	
Vomiting					
No	29 (37.2)	49 (62.8)	1 (Reference)	1 (Reference)	0.51
Yes	25 (24.8)	76 (75.2)	1.80 (0.95–3.43)	1.33 (0.37–3.08)	
Persistent vomiting					
No	41 (33.9)	80 (66.1)	1 (Reference)	1 (Reference)	0.06
Yes	13 (22.4)	45 (77.6)	1.77 (0.86–3.66)	2.56 (0.97–6.75)	
Liver enlargement					
No	45 (32.1)	95 (67.9)	1 (Reference)	1 (Reference)	0.18
Yes	9 (23.1)	30 (76.9)	1.58 (0.69–3.60)	1.90 (0.75–4.85)	
Mucosal bleeding					
No	36 (29.8)	85 (70.2)	1 (Reference)	1 (Reference)	0.32
Yes	18 (31.0)	40 (69.0)	0.94 (0.48–1.86)	0.67 (0.30–1.48)	

OR: odds ratio
CI: confident interval
[a]Adjusted for all variables listed in the table.
[b]Hospital includes district hospitals and the provincial hospital.
[c]Other includes private clinics and health care centers.
*P <0.05

Table 4 Association between socio-demographic factors and clinical signs on admission with sever dengue in adults

Variables	Non-severe dengue (N=143)	Severe dengue (N=80)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]	*P*-value
	n (%)	n (%)			
Age group (years)					
15–24	74 (59.2)	51 (40.8)	1 (Reference)	1 (Reference)	
25–44	57 (67.1)	28 (32.9)	0.71 (0.41–1.27)	0.85 (0.42–1.71)	0.65
45–82	12 (92.3)	1 (7.7)	0.12 (0.01–0.96)*	0.09 (0.01–1.06)	0.06
Sex					
Male	79 (66.4)	40 (33.6)	1 (Reference)	1 (Reference)	0.44
Female	64 (61.5)	40 (38.5)	1.23 (0.71–2.13)	1.28 (0.69–2.38)	
Occupation					
Student	74 (66.1)	38 (33.9)	1 (Reference)	1 (Reference)	0.97
Other[b]	69 (62.2)	42 (37.8)	1.71 (0.96–3.09)	1.01 (0.50–2.05)	
Use of health facilities before admission					
No	77 (66.4)	39 (33.6)	1 (Reference)	1 (Reference)	0.28
Yes	66 (61.7)	41 (38.3)	1.22 (0.71–2.12)	1.44 (0.74–2.81)	
Clinical symptoms and signs on admission					
Fever					
No	112 (64.7)	61 (35.3)	1 (Reference)	1 (Reference)	0.47
Yes	31 (62.0)	19 (38.0)	1.12 (0.59–2.15)	1.41 (0.55–3.57)	
Tourniquet test					
(–)	22 (56.4)	17 (43.6)	1 (Reference)	1 (Reference)	0.31
(+)	121 (65.8)	63 (34.2)	0.67 (0.33–1.36)	0.67 (0.30–1.46)	
Skin rash					
No	132 (63.5)	76 (36.5)	1 (Reference)	1 (Reference)	0.24
Yes	11 (73.3)	4 (26.7)	0.63 (0.19–2.05)	0.42 (0.10–1.79)	
Headache					
No	6 (85.7)	1 (14.3)	1 (Reference)	1 (Reference)	0.17
Yes	137 (63.4)	79 (36.6)	3.46 (0.34–2.44)	5.73 (0.48–69.27)	
Myalgia					
No	12 (66.7)	6 (33.3)	1 (Reference)	1 (Reference)	0.64
Yes	131 (63.9)	74 (36.1)	1.13 (0.40–3.13)	0.74 (0.20–2.72)	
General body ache					
No	21 (56.8)	16 (43.2)	1 (Reference)	1 (Reference)	0.09
Yes	122 (65.6)	64 (34.4)	0.69 (0.34–1.41)	0.46 (0.18–1.14)	
Arthralgia					
No	49 (67.1)	24 (32.9)	1 (Reference)	1 (Reference)	0.70
Yes	94 (62.7)	56 (37.3)	1.22 (0.67–2.19)	0.87 (0.44–1.74)	

Nausea					
No	67 (63.2)	39 (36.8)	1 (Reference)	1 (Reference)	0.14
Yes	76 (65.0)	41 (35.0)	0.93 (0.53–1.60)	0.55 (0.25–1.29)	
Anorexia					
No	91 (66.9)	45 (33.1)	1 (Reference)	1 (Reference)	0.57
Yes	52 (59.8)	35 (40.2)	1.36 (0.77–2.38)	1.21 (0.62–2.38)	
Severe abdominal pain					
No	80 (65.6)	42 (34.4)	1 (Reference)	1 (Reference)	0.17
Yes	63 (62.4)	38 (37.6)	1.14 (0.66–2.00)	0.54 (0.22–1.31)	
Vomiting					
No	85 (65.9)	44 (34.1)	1 (Reference)	1 (Reference)	0.40
Yes	58 (61.7)	36 (38.3)	1.20 (0.70–2.08)	1.44 (0.62–3.37)	
Persistent vomiting					
No	135 (67.5)	65 (32.5)	1 (Reference)	1 (Reference)	0.02
Yes	8 (34.8)	15 (65.2)	3.89 (1.57–9.65)**	3.82 (1.23–11.92)	
Pleural effusions					
No	140 (65.1)	75 (34.9)	1 (Reference)	1 (Reference)	0.33
Yes	3 (37.5)	5 (62.5)	3.11 (0.72–13.37)	2.47 (0.41–14.89)	
Mucosal bleeding					
No	111 (67.3)	54 (32.7)	1 (Reference)	1 (Reference)	0.42
Yes	32 (55.2)	26 (44.8)	1.67 (0.90–3.07)	1.34 (0.66–2.74)	
Dizziness					
No	105 (68.2)	49 (31.8)	1 (Reference)	1 (Reference)	0.14
Yes	38 (55.1)	31 (44.9)	1.75 (0.98–3.13)	1.97 (0.81–4.81)	

OR odds ratio
CI: confident interval
[a]Adjusted for all variables.
[b]Other includes farmer, self-employee, officer, and no work.
*P <0.05, **P <0.01

To identify factors associated with the final diagnosis of severe dengue, age, sex, and clinical signs on admission were analyzed in children and adults. Regarding pediatric patients, bivariate logistic regression analysis showed that the diagnosis of severe dengue was significantly higher in those who had nausea on admission (crude OR = 2.94, P = 0.041) than in those who did not (Table 3). Multiple logistic regression analysis adjusted for all factors showed that nausea (adjusted OR = 3.57, 95% CI = 1.05–12.09, P = 0.04) on admission was significantly associated with the final diagnosis of severe dengue. In the forward and backward stepwise selection methods, only nausea was associated with the final diagnosis of severe dengue.

Among patients aged ≥15 years, those aged 45–82 years (crude OR = 0.12, P = 0.046) had significantly less severe dengue than those aged 15–24 years, and persistent vomiting symptom (crude OR = 3.89, P = 0.003) on admission was significantly associated with severe dengue (Table 4). After adjusting for all variables, only persistent vomiting on admission (adjusted OR = 3.82, 95% CI = 1.23–11.92, P = 0.02) was found to have a significant impact on the incidence

of severe dengue among adult patients. The result of forward stepwise regression was the same as that of the forced-entry method. In the backward stepwise method, two variables were associated with the final diagnosis of severe dengue: the age group of 45–82 years compared to 15–24 years (adjusted OR = 8.14, 95% CI = 1.00–66.13, P = 0.0497) and persistent vomiting (adjusted OR = 3.79, 95% CI = 1.49–9.61, P = 0.005) showed significant differences in the final diagnosis of severe dengue.

All patients underwent complete blood count tests, but only nine children and 97 adults underwent biochemical tests (Table 5). The t-test was performed to compare the results of blood tests of patients who were finally diagnosed with non-severe and those diagnosed with severe dengue. Children with severe dengue had a higher level of hemoglobin and lower level of platelet than children with non- severe dengue, but the differences were not significant. Adults with severe dengue were more likely to have a lower level of platelet than those with non-severe dengue, but the difference was not significant. The levels of hemoglobin and hematocrit were almost the same among the two groups of patients. As per the biochemistry tests, the level of creatinine in adult patients was significantly higher in the severe dengue than in the non-severe dengue group (P = 0.04). The levels of ALT and AST were lower in the severe dengue than in the non-severe dengue group, but not at a significant level.

Table 5 Comparison of laboratory data on admission in children and adults

Laboratory examination	Non-severe dengue			Severe dengue			P-value
	N	Mean	(SD)	N	Mean	(SD)	
Children							
Hemoglobin (g/dL)	179	11.4	(2.1)	125	12.8	(4.3)	0.90
Hematocrit (%)	179	37.0	(5.1)	125	38.9	(7.0)	0.13
Platelet ($\times 10^3/\mu L$)	179	91.0	(55.7)	125	77.2	(54.5)	0.91
Glucose (mg/dL)	9	97.0		8	102.6	(19.7)	-
Creatinine (mg/dL)	3	1.0		2	1.1	(0.5)	-
ALT (U/L)	4	97.0		3	130.2	(142.9)	-
AST (U/L)	4	337.0		3	113.2	(66.0)	-
Adults							
Hemoglobin (g/dL)	223	13.0	(7.3)	80	13.0	(3.9)	0.82
Hematocrit (%)	223	40.0	(7.5)	80	39.6	(6.7)	0.47
Platelet ($\times 10^3/\mu L$)	223	92.5	(69.0)	80	84.7	(78.8)	0.93
Glucose (mg/dL)	97	103.7	(25.7)	36	105.6	(28.6)	0.90
Creatinine (mg/dL)	82	1.0	(0.3)	36	2.0	(6.7)	0.04
ALT (U/L)	31	108.9	(94.3)	18	102.3	(83.0)	0.89
AST (U/L)	31	153.7	(142.2)	18	114.0	(82.5)	0.22

SD: standard deviation
ALT: alanine aminotransferase
AST: aspartate aminotransferase

DISCUSSION

The number of inpatients with dengue was higher in the rainy season than in the dry season. The hot and humid weather of the monsoons is a condition favorable for mosquito (*Aedes* species) breeding, which is associated with dengue outbreaks.[7,20]

In this study, the proportion of final diagnosis of severe dengue was 51.0% among dengue patients admitted to the Savannakhet Provincial Hospital between January 2018 and April 2019, which was higher than that in previous studies in other Asian countries: 35% in inpatients in India,[21] and 28% in Singapore.[22] In a systematic review comprising 198 studies, the proportion of severe dengue was 28.5%.[23] This is probably because all dengue patients in severe conditions in all 14 districts of Savannakhet Province were referred to the provincial hospital. There might have been a delay in visiting the health care facilities owing to the rainy season or lack of transportation in rural areas,[24,25] although patients seemed to understand that they should visit health facilities when they were suffered.[26] The limited number of health care workers and the low level of health care at health centers and district hospitals might have led to severe condition. Furthermore, the referral system from lower levels to high levels in public health facilities might have been another reason for the high incidence of severe dengue because some districts have no ambulance service.

Children showed significantly more clinical symptoms and signs on admission than adults. The mean hospitalization and incidence of severe dengue were also significantly longer and higher in children than in adults, respectively. These results were consistent with those of previous studies in Asian countries as well as a systemic review.[23] This finding could be attributed to the fact that the protective immune responses to secondary infections are less developed and microvascular fragility is higher in children than in adults.[21-23,27]

In pediatric patients in this study, nausea on admission was significantly associated with the final diagnosis of severe dengue. This result was consistent with the results of previous studies.[22,23,28] In adult patients, young age and persistent vomiting on admission were significantly associated with the final diagnosis of severe dengue. This result was consistent with those of previous studies, which reported that persistent vomiting was a good predictor of severe plasma leakage and a factor associated with severe dengue.[21-23,27] Laboratory data in this study showed that the creatinine level was significantly higher in severe dengue than in non-severe dengue patients. AKI is a common complication of severe dengue and patients with AKI have longer hospitalization and higher mortality than non-AKI patients.[28,29]

To treat severe dengue patients appropriately, a treatment team for dengue in hospitals must carefully monitor and assess dengue patients who exhibit plasma leakage. However, it seemed that members of the treatment team in the provincial hospital did not accurately follow the guideline because the number of admitted patients was high but the nursing staff were not enough. It is also reported that healthcare workers do not follow the guidelines when they do not understand about the guidelines.[30,31] Severe dengue patients should be monitored in the intensive care unit rather than in the general wards.[12,32] These results suggest that strict adherence to guidelines by healthcare workers and sufficient medical staff are necessary for treating severe dengue patients.

To reduce the incidence of severe dengue and CFR of dengue in Lao PDR, the Ministry of Health and WHO recommend daily reporting of suggested cases to the Emergency Operating Center and retraining treatment teams in health facilities at the provincial, district, and health center levels. The recommended training program includes (1) physiology of dengue according to the three phases of dengue and (2) diagnosis, classification, and treatment indicators, e.g., dengue patients can stay at home with symptomatic treatment when they have no warning signs, but patients with warning signs are recommended to be hospitalized, observed carefully in the

hospital, and must be referred to a provincial hospital. Severe dengue patients should be admitted to the intensive care unit in provincial hospitals. (3) Patient follow-up and assessment should be carried out according to the standard guidelines. (4) Treatment should be based on the WHO guidelines on dengue classification, diagnosis, treatment, and control. Training should be provided to healthcare teams every year, and the surveillance and referral systems should be improved.

This study had some limitations. First, the incidence of severe dengue might be underestimated. Some patients were discharged against medical advice and their outcomes were unknown. It was reported that there were 12 dengue-related deaths in Savannakhet Province from January 2018 to April 2019. However, death cases could not be included because medical records of all death cases had been sent to the Ministry of Health for further analyses and not available for inclusion in this study. If the outcome and data of these patients were collected, the factors associated with death due to dengue could have been studied. Second, the clinical signs and diagnosis might not have been diagnosed correctly. Only four children and 82 adults underwent blood examinations for liver and kidney functions on admission for diagnosis of acute liver failure and AKI. In the hospital, magnetic resonance imaging for the diagnosis of encephalopathy or encephalitis was not available. However, this study included many clinical symptoms and results of complete blood count tests. Therefore, risk factors for severe dengue outlined in this study may be useful for doctors in provinces of Lao PDR and other developing countries. Third, this study did not include a history of dengue and the serotype of dengue in variables of analyses, although these factors were suggested to be associated with severe dengue. Further studies on outcomes, laboratory data, treatment during hospitalization, and history of dengue are warranted to determine the factors associated with severe dengue and dengue outbreaks in Lao PDR.

In conclusion, the incidence of severe dengue was 51.0% among inpatients at the Savannakhet Provincial Hospital and it was higher than that in other Asian countries. Children had more symptoms, longer hospitalization duration, and higher incidence of severe dengue than adults. In children, nausea was associated with severe dengue. In adults, persistent vomiting on admission was associated with severe dengue and the creatinine level on admission was higher in severe dengue than non-severe dengue. These results suggest that nausea and persistent vomiting are predictive factors for severe dengue. To reduce the incidence of severe dengue, training programs on management of dengue patients should be provided to healthcare workers and the referral system should be improved in Lao PDR.

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CONFLICTS OF INTEREST

The authors have nothing to disclose.

REFERENCES

1 Bhatt S, Gething PW, Brady OJ, et al. The global distribution and burden of dengue. *Nature*. 2013;496(7446):504–507.

2 WHO, Regional Office for South-East Asia. *Comprehensive Guideline for Prevention and Control of Dengue and Dengue Haemorrhagic Fever*. Revised and expanded ed. New Delhi: World Health Organization; 2011.
3 Tien Dat T, Kotani T, Yamamoto E, et al. Dengue fever during pregnancy. *Nagoya J Med Sci*. 2018;80(2):241–247.
4 WHO. *Global strategy for dengue prevention and control 2012–2020*. Geneva: World Health Organization; 2012.
5 Shepard DS, Undurraga EA, Halasa YA. Economic and disease burden of dengue in Southeast Asia. *PLoS Negl Trop Dis*. 2013;7(2):e2055. doi:10.1371/journal.pntd.0002055.
6 Limkittikul K, Brett J, L'Azou M. Epidemiological trends of dengue disease in Thailand (2000–2011): a systematic literature review. *PLoS Negl Trop Dis*. 2014;8(11):e3241. doi:10.1371/journal.pntd.0003241.
7 WHO. *Dengue increase likely during rainy season: WHO warns*. https://www.who.int/westernpacific/news/detail/11-06-2019-dengue-increase-likely-during-rainy-season-who-warns. Published 2019. Accessed July 31, 2020.
8 Guzman MG, Halstead SB, Artsob H, et al. Dengue: a continuing global threat. *Nat Rev Microbiol*. 2010;8(12 Suppl):S7–S16.
9 WHO. *Dengue: guidelines for diagnosis, treatment, prevention and control*. New ed. Geneva: World Health Organization; 2009.
10 WHO and Special Programme for Research and Training in Tropical Diseases. *Handbook for clinical management of dengue*. Geneva: World Health Organization; 2012.
11 WHO. *Dengue haemorrhagic fever : diagnosis, treatment, prevention and control*. Geneva: World Health Organization; 1997.
12 Kalayanarooj S. Clinical Manifestations and Management of Dengue/DHF/DSS. *Trop Med Health*. 2011;39(4 Suppl):83–87.
13 Reich NG, Shrestha S, King AA, et al. Interactions between serotypes of dengue highlight epidemiological impact of cross-immunity. *J R Soc Interface*. 2013;10(86):20130414.
14 Vuong NL, Manh DH, Mai NT, et al. Criteria of "persistent vomiting" in the WHO 2009 warning signs for dengue case classification. *Trop Med Health*. 2016;44:14.
15 Louangpradith V, Phoummalaysith B, Kariya T, Saw YM, Yamamoto E, Hamajima N. Disease frequency among inpatients at a tertiary general hospital in Lao PDR. *Nagoya J Med Sci*. 2020;82(1):113–121.
16 Ministry of Health, National Central Laboratory and Epidemiology. *Dengue Annual Report*. Vientiane Capital: Ministry of Health; 2019.
17 Mayxay M, Phetsouvanh R, Moore CE, et al. Predictive diagnostic value of the tourniquet test for the diagnosis of dengue infection in adults. *Trop Med Int Health*. 2011;16(1):127–133.
18 Fleming S, Gill PJ, Van den Bruel A, Thompson M. Capillary refill time in sick children: a clinical guide for general practice. *Br J Gen Pract*. 2016;66(652):587.
19 Samanta J, Sharma V. Dengue and its effects on liver. *World J Clin Cases*. 2015;3(2):125–131.
20 Pasin C, Halloran ME, Gilbert PB, et al. Periods of high dengue transmission defined by rainfall do not impact efficacy of dengue vaccine in regions of endemic disease. *PLoS One*. 2018;13(12):e0207878. doi:10.1371/journal.pone.0207878.
21 Agrawal VK, Prusty BSK, Reddy CS, Mohan Reddy GK, Agrawal RK, Sekher Srinivasarao Bandaru VC. Clinical profile and predictors of Severe Dengue disease: A study from South India. *Caspian J Intern Med*. 2018;9(4):334–340.
22 Carrasco LR, Leo YS, Cook AR, et al. Predictive tools for severe dengue conforming to World Health Organization 2009 criteria. *PLoS Negl Trop Dis*. 2014;8(7):e2972. doi:10.1371/journal.pntd.0002972.
23 Huy NT, Van Giang T, Thuy DH, et al. Factors associated with dengue shock syndrome: a systematic review and meta-analysis. *PLoS Negl Trop Dis*. 2013;7(9):e2412. doi:10.1371/journal.pntd.0002412.
24 Chankham T, Yamamoto E, Reyer JA, et al. Knowledge of free delivery policy among women who delivered at health facilities in Oudomxay Province, Lao PDR. *Nagoya J Med Sci*. 2017;79(2):135–145.
25 Phoummalaysith B, Yamamoto E, Xeuatvongsa A, et al. Factors associated with routine immunization coverage of children under one year old in Lao People's Democratic Republic. *Vaccine*. 2018;36(19):2666–2672.
26 Nalongsack S, Yoshida Y, Morita S, Sosouphanh K, Sakamoto J. Knowledge, attitude and practice regarding dengue among people in Pakse, Laos. *Nagoya J Med Sci*. 2009;71(1–2):29–37.
27 Guzman MG, Alvarez M, Rodriguez R, et al. Fatal dengue hemorrhagic fever in Cuba, 1997. *Int J Infect Dis*. 1999;3(3):130–135.
28 Sirivichayakul C, Limkittikul K, Chanthavanich P, et al. Dengue infection in children in Ratchaburi, Thailand: a cohort study. II. Clinical manifestations. *PLoS Negl Trop Dis*. 2012;6(2):e1520. doi:10.1371/journal.pntd.0001520.

29 Oliveira JF, Burdmann EA. Dengue-associated acute kidney injury. *Clin Kidney J*. 2015;8(6):681–685.
30 Keohavong B, Vonglokham M, Phoummalaysith B, et al. Antibiotic prescription for under-fives with common cold or upper respiratory tract infection in Savannakhet Province, Lao PDR. *Trop Med Health*. 2019;47:16.
31 Inthanomchanh V, Reyer JA, Blessmen J, Phrasisombath K, Yamamoto E, Hamajima N. Assessment of knowledge about snakebite management amongst healthcare providers in the provincial and two district hospitals in Savannakhet Province, Lao PDR. *Nagoya J Med Sci*. 2017;79(3):299–311.
32 Pang J, Thein TL, Leo YS, Lye DC. Early clinical and laboratory risk factors of intensive care unit requirement during 2004–2008 dengue epidemics in Singapore: a matched case-control study. *BMC Infect Dis*. 2014;14:649.