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Research Article

Prognostic Factors of Severe Dengue Infections in Children

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ABSTRACT

The incidence of dengue fever increase annually and can increase morbidity and mortality. Dengue fever is mosquito-borne disease and caused by one of four serotype dengue viruses. Severe dengue is characterized either by plasma leakage, fluid accumulation, respiratory distress, severe bleeding, or organ impairment. Mortality and serious morbidity of dengue were caused by several factors including the late recognition of the disease and the changing of clinical signs and symptoms. Understanding the prognostic factors in severe dengue will give early warning to physician thus decreasing the morbidity and mortality, and also improving the treatment and disease management. The aim of this study was to analyze the prognostic factors of severe dengue infection in children. This study was observational cohort study in children (2 months-18 years) with dengue infection according to WHO 2009 criteria which admitted in Soetomo and Soewandhie Hospital Surabaya. Analysis with univariate, bivariate and multivariate with IBM SPSS Statistic 17. All patients were confirmed by serologic marker (NS-1 or IgM/IgG Dengue). Clinical and laboratory examination such as complete blood count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, and both partial trombocite time and activated partial trombosit time (PTT and aPPT) were analyzed comparing nonsevere dengue and severe dengue patients. There were 40 subjects innonsevere and 27 subjects with severe dengue infection. On bivariate analysis, there were significant differences of nutritional status, abdominal pain, petechiae, pleural effusion, leukopenia, thrombocytopenia, hypoalbuminemia, history of transfusion, increasing AST > 3x, prolonged PPT and APTT between severe and nonsevere dengue group. After multivariate analyzed, the prognostic factors of severe dengue were overweight/obesity (p=0.003, RR 94), vomiting (p=0.02, RR 13.3), hepatomegaly (p=0.01, RR=69.4), and prolonged APTT (p=0.005, RR=43.25). In conclusion, overweight/obesity, vomiting, hepatomegaly, and prolonged APTT were prognostic factors in severe dengue infection in children. Those factors should be monitored closely in order to reduce the mortality and serious morbidity.

Keywords: *Severe dengue, dengue infection, increased APTT, overweight/obesity, hepatomegaly*

ABSTRAK

Dengue merupakan penyakit virus yang disebabkan oleh satu dari empat serotipe virus dengue dan ditularkan oleh nyamuk. Kasus dengue berat berdasarkan kriteria WHO 2009 di definisikan sebagai dengue dengan satu atau lebih kondisi berikut; kebocoran plasma yang menyebabkan syok (dengue syok) dan atau akumulasi cairan dengan distres nafas, perdarahan berat dan yang ketiga adalah keterlibatan organ. Diagnosa dini bermanfaat menurunkan morbiditas dan mortalitas, managemen klinis, surveilans dan control penyakit serta menurunkan durasi rawat inap. Penelitian ini menganalisis faktor prognosis infeksi dengue berat pada anak. Kohortobservasional pada pasien usia 2 bulan-18 tahun dengan infeksi dengue berdasarkan kriteria WHO 2009 yang MRS ataupun di poliklinik rawat jalan di RSUD DR. Soetomo dan RSUD Soewandhie Surabaya. Analisis data dilakukan dengan univariat, bivariate dan multivariate menggunakan IBM SPSS Statistic 17. Semua pasien terkonfirmasi dengan pemeriksaan serologis (NS-1 atau IgM/IgG Dengue). Data klinis dan laboratorium (darah lengkap, AST, ALT, albumin, APTT dan PPT) dianalisis untuk membandingkan antara kelompok dengue tidak berat dan dengue berat. Sebanyak 40 subyek pada kelompok infeksi dengue tidak berat dan 27 subyek pada kelompok dengue berat yang memenuhi

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kriteria inklusi. Didapatkan perbedaan yang bermakna berdasarkan analisis bivariate pada variabel Overweight/obesitas, nyeri perut, efusi pleura, hepatomegali, leukopeni, trombositopenia, hipoalbuminemia, AST meningkat>3x, PPT dan APTT meningkat serta riwayat transfusi. Overweight/obesitas (p=0.003, 95% RR 94), muntah (p=0.02, RR 13.3), hepatomegali (p=0.01, RR=69.4), dan pemanjangan APTT (p=0.005, RR=43.25) merupakan faktor prognosis infeksi dengue berat berdasarkan analisis multivariat. Status nutrisi, muntah, hepatomegali dan pemanjangan APTT merupakan faktor prognostik infeksi dengue berat pada anak. Monitoring terhadap factor tersebut perlu dilakukan untuk menurunkan mortalitas dan morbiditas.

Kata kunci: *Dengue berat, infeksi dengue, peningkatan APTT, overweight/obesitas, hepatomegaly*

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INTRODUCTION

The worldwide prevalence of dengue fever is estimated 50 -100 billion and dengue hemorrhagic fever about 250.000-500.000.[1] Incidence of DHF over the past 45 years in Indonesia increased rapidly.[2] Dengue fever is mosquito-borne disease and caused by one of four serotype dengue viruses. This four serotype are dengue virus serotype-1 (DENV-1), serotype-2 (DENV-2), serotype-3 (DENV-3), and serotype-4 (DENV-4). Dengue infection is characterized by fever and constitutional symptoms to hemorrhagic manifestations and shock, or dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS). The most serious spectrum of this disease, severe dengue, is characterized either by plasma leakage, fluid accumulation, respiratory distress, severe bleeding, or organ impairment.[1,3] Clinical manifestations of dengue fever are the expression of host and viral factors, some acquired, others intrinsic to the individual. The virulence of the virus and the flavivirus infection history, age, gender and genotype of the host can determine to severity of the disease.[4] The warning signs in dengue usage was proposed for early detection of potentially severe cases for timely treatment, to avoid unnecessary hospitalizations, and to decrease the case fatality of the disease.[1,5] Early prediction of severe dengue in patients without any warning signs who might later develop severe dengue is very important to give the best supportive.[6] Patients should be monitored by health care providers for temperature pattern, volume of fluid intake and losses, urine output (volume and frequency), warning signs, haematocrit, and white blood cell and platelet counts.[1]

The rapidly expanding global footprint of dengue is a public health challenge with an economic burden that is currently unmet by licensed vaccines, specific therapeutic agents, or efficient vectorcontrol strategies.[3] There are several signs and symptoms called warning signs that can be used to predict severe dengue, hence recognizing the warning signs is important for successful clinical management. Warning signs include abdominal pain, evidence of fluid accumulation, hepatomegaly and increases in hematocrit accompanied by a fall in the platelet count.[2]

The benefit of prompt diagnosis is decreasing morbidity and mortality, improving treatment and surveillance, and also enhancing disease management.[7,8] Early diagnosis of dengue infection can improved by algorithms using early clinical indicators. Indicator addition of severe plasma leakage to WHO definition led to increase the sensitivity using White Blood Cells (WBC), AST, platelet count and age.[9] A retropsective study by Nguyen *et al*, reported the final prognostic model included history of vomiting, platelet count, AST level and NS1 rapid test.[10] We were conducted prospective study to evaluation prognostic factors in severe dengue infection in children.

MATERIALS AND METHODS

This was a cohort observational study. The study population was the patient in the pediatric outpatient clinic and pediatric emergency department at Dr. Soetomo Hospital and Soewandhie Hospital in Surabaya. The minimal sample requirements were 26 based on the formula by Lemeshow. Subject eligible between two months until 18 years old with fever ≥ 3 days and probable dengue infection symptoms such as headache, nausea-vomiting, petechiae, arthralgia, and retro-orbital pain were included. Patients were assessed as severe dengue and non-severe dengue based on WHO 2009 guideline and positively serology marker such as IgM or antigen non structural-1 (NS-1). The WHO 2009 Guideline mentioned the severe dengue as either by plasma leakage, fluid accumulation, respiratory distress, severe bleeding, or organ impairment.[5] The exclusion criteria were a congenital anomaly, malignancy, autoimmune and immunodeficiency disease because the clinical signs and symptoms, and the laboratory test results of those diseases can mimic or influence the clinical and laboratory pictures of severe dengue patients. We also performed chest X ray examination to distinguish pleural effusion when patients admission.

Nutritional status was assessed by BMI CDC growth chart 2000 for patients 2-18 years old and WHO 2007b for patient below than 2 years old. The data were analyzed by the Statistical Program for Social Science software (SPSS) IBM SPSS windows Statistic 17.0. Chi-square test was used to assess the categorical data and logistic regression carried out to evaluate multivariate analysis.

In this study, laboratory examination was carried out from the material of venous blood samples by using Hematology Analyzer Sysmex XN1000 and Celldyne Ruby Sysmex CS2100 to analyze complete blood count, Siemens Dimension to analyze albumin, AST and ALT. while *Sysmex* CS2100 to analyzed PPT and APTT. For repeated tests, we use the worst results before the severe condition. This study was approved by both Health Research Ethical Committee of Dr. Soetomo and Soewandhie Hospital (Document no. 640/Panke.KKE/XI/2017 date: November 13th 2017-November 13th 2018 and no. 070/12334/436.8.6/2018 date : Mei 23rd 2018).

RESULTS AND DISCUSSION

During the eight-month period of the study, a total of 67 patients with dengue infection met the inclusion criteria, in which 27 and 40 were diagnosed as severe dengue and non-severe dengue infection, respectively. All patients were confirmed by serologic marker (NS-1 or IgM/IgG Dengue). All subjects were carried out anamnesis, physical examination, and laboratory. Clinical and laboratory examination (complete blood count, AST, ALT, albumin, APTT, and PPT) were analyzed comparing non-severe dengue and severe dengue patients. Figure 1.

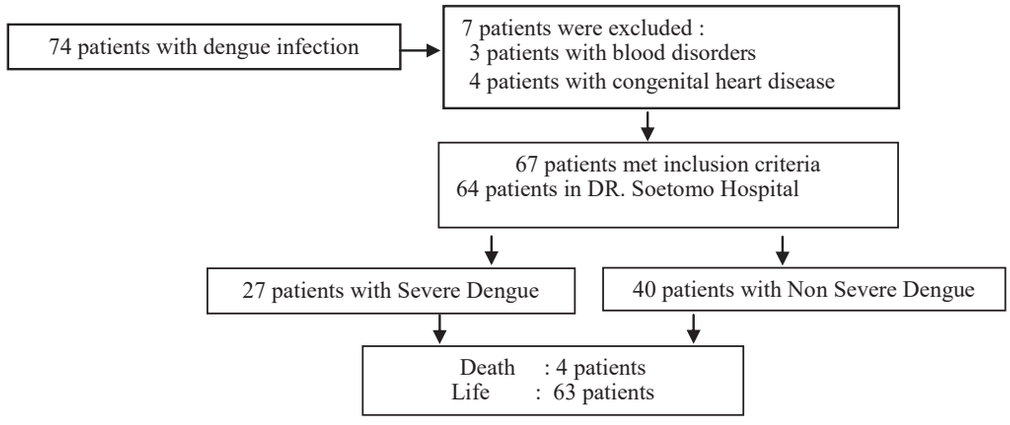

Figure 1. Flow Diagram of Subject Recruitment.

Table 1. Baseline Characteristic

Characteristics		Groups		P value
		Severe Dengue n=27 (%)	**Non Severe Dengue n=40 (%)**	
Age,(year)	≤ 5 years	4 (14.8)	7(17.5)	0.77
	>5 years	23 (82.5)	33 (82.5)	
Gender, n(%)	Male	14 (43.8)	18 (56.3)	0.76
	Female	13 (37.1)	22 (62.9)	
Referral, n(%)	Yes	18 (66.7)	17 (42.5)	0.052
	No	9 (33.3)	23 (57.5)	
Nutritional State				
Non *Overweight*/Obesity		12 (24.0)	38 (76.0)	**<0.001***
***Overweight*/Obesity**		15(88.2)	2 (11.8)	
DOI (*day of Illness*)(day)		2-6	2-6	
LOS (*length of Stay*)(day)	Duration	1-11 (day)	2-8 (hari)	
Outcome	Life	23 (85.2)	40 (100)	**0.012***
	Death	4 (14.8)	0 (0)	

describe row diagram of subject recruitment in this study. Characteristics of 67 research subjects can be seen in Table 1. On bivariate analysis, there were significant differences of thrombocytopenia, hypoalbuminemia, history of transfusion, increasing AST>3x, nutritional status, abdominal pain, petechiae, pleural effusion, leucopenia, prolonged PPT and APTT between severe and non-severe dengue groups. After multivariate analyzed, the prognostic factors of severe dengue were overweight/obesity (p=0.003, RR 94), vomiting (p=0.02, RR 13.3), hepatomegaly (p=0.01, RR=69.4), dan prolonged APTT (p=0.005, RR=43.25).

The baseline characteristics of children with dengue infection and controls in this study were very similar except nutritional status and outcome. Age ≤ 5 years in severe dengue were 14.8% and 82.5% in subject more than 5 years old (>5 years). Non severe dengue were more common in subject > 5 years old (82.5%) than subjects with age ≤ 5 years (17.5%). Male to female proportion in severe dengue were 43.8% and 37.1% , non severe dengue were 56.3% and 62.9% respectively. Referral subjects with severe dengue were 66.7% and non Referral were 33.3%. While more than half of subjects with non severe dengue (57.3%) came to Soetomo Hospital by itself and 42.5% were referral from other hospital. Nutritional status was statistic significantly in bivariate and multivariate analysis (RR 2.93, 95% CI 2.18-6.20) whereas the previous study by Maron *et al* and Yulianto *et al* and Ledika *et al,* Excess nutrition does not appear to be a risk factor for severe dengue infection.[11,12,13] In addition, normal nutritional status had negative correlation with DHF and DSS.[14] However, meta-analysis and systematic review recently enroled 15 studies from 2000 until 2016 reported obesity as a risk factor of severity in children with dengue infection (OR = 1.38; 95% CI:1.10, 1.73).[15] In addition, recent study shown obese patients with dengue infection possess many clinical parameters suggestive of more severe clinical manifestations.[16] Study of obesity in severe dengue infection still rare. Leptin is a major mediator of the altered immune balance in the obese individuals and has been shown to promote macrophage phagocytosis, increase secretion of pro-inflammatory cytokines and modulate the adaptive immune system. Elevated leptin and SOCS3 levels correlates with a decreased type

1 interferon response, which serves as a crucial innate immune system activator in stimulating an antiviral state.[17]

Severe dengue group in this study had a prolonged length of stay (1-11 days) than non-severe dengue group (2-8 days). The mortality rate in this study was 5.9% in all subjects and 50% were severe dengue patients with obesity, while other study by Patrayusha *et al*[18] reported mortality rate was 6.25% and 1.03% in Mishra *et al*[19] Mortality of DHF or DSS estimated 40-50% in pitfall management. However WHO was stated management properly can save lives and mortality rates from more than 20% to less than 1%.[1]

The proportion of severe dengue and non-severe dengue with vomiting were 88.9% and 70% respectively. Vomiting more common in DSS and expanded dengue syndrome than non-severe dengue with frequent variously range 3-5x/day. In the previous study was reported the prevalence of vomiting symptom was higher in severe dengue group than dengue infection/dengue infection with warning sign group.[20] Persistent vomiting is one warning sign according to WHO 2009.[1] Ledika *et al* held study in patients with severe dengue showed persistent vomiting had correlated with severe dengue.[13] Meta analysis study by Zhang *et al* was reported nausea-vomiting, as the predictor of severe dengue in children. Vomiting was often found in dengue patients, especially in children. Vomiting could cause fluid imbalance and also difficulty in assessing the hydration state of the patient.[21]

In present study, abdominal pain in severe dengue was 85% while in non severe dengue groups about 45%. Despite statistic significantly from bivariate analysis (p= 0.002, RR 3.6) however from the regression logistic shown unsignificantly. Abdominal pain is one of warning sign in dengue infection and epigastrium pain is sign of dengue hemorrhagic fever.[1] Meta analysis study by Zhang *et al* was stated abdominal pain could predict of severe dengue infection.[21] The mechanism of abdominal pain in dengue infection was unknown. Gupta *et al* was reported the most common specific cause of acute abdominal pain was acute hepatitis,[22] previously Shabir *et al* was reported proportion of abdominal pain was 32% and liver involvement was the common cause of abdominal pain in dengue fever.[23]

In present study, bleeding manifestation presented with epistaxis, ptechie, melena and hematemesis. In addition, proportion of *torniquet* test were very similar in severe dengue and non severe dengue group (92.6% and 100%). Melena in severe dengue group was 14.48% and 2.5% in non severe dengue group. Both of bivariate and multivariate analysis revealed statistic unsignificantly (p= 0.16 and 0.14 respectively in Table. 2 and Table. 3). Epistaksis found in 3 patients with severe dengue (11.1%) and 7 patients with non severe dengue (17.5%) while ptechie more common in severe dengue than non severe dengue patients (66.7% and 35%). Epistaxis and ptechie occurred in 3-5 days of illness. Whereas, hematemesis occurred in 2 patients with severe dengue (7.4%) and 1 patients with non severe dengue (2.5%). Statistic unsignificantly noticed in bivariate analysis (p= 0.73 in Table. 2). Bleeding (hematemesis or melena) occurred in 5-7 day of illness. Melena range from 50cc-1000cc and leading to hemodinamic imbalance. Two patients with severe dengue required whole blood transfusion. In this study, massif bleeding and profound shock due to hematemesis and melena leading to mortality in two patient with severe dengue.

In this study, transfusion administration in 9 patients with severe dengue. Whole blood and PRC were given in patients with bleeding and hemodinamic disturbance with previous colloid and crystaloid administration. FFP was given in patients with prolonged APTT and bleeding manifestation (hematemesis and melena). All of them accompanied with trombocytophenia (<50000/μL) and 7 patients with increasing of AST (>200-12186 U/L). Five patients with decreasing of Hemoglobine and hematocrit also accompanied prolonged shock. All of subject with transfusion were severe dengue group.

The most common spontaneous bleeding sign in dengue infection was ptechie. Prathyusha *et al* was shown that ptechie occurred in 70% in children with dengue infection.[18] While Branco *et al* was reported that epistaxis, hemoptisis and persistent vomiting associated with mortality

in children with dengue infection.[24] Zhang was reported that patients with bleeding after DENV infection had approximately a 14-fold increased risk for progression into severe dengue (including DHF and DSS). According to this meta-analysis, the two kinds of gastrointestinal bleeding that strongly predicted severe dengue were hematemesis and melena.[21] Otherwise, *torniquet* test and petechiae not significant associated with severe dengue. A positive *tourniquet* test in febrile phase increases the probability of dengue but indistinguishable between severe and non severe dengue case.[1]

Previously, Pongpan *et al* was reported thrombocytopenia (≤50.000 mm^3) as prognostic factor severe dengue in children,[10] in addition some studies by Ledika *et al*[13] and Yulianto *et al*[12] were reported thrombocytopenia as risk factor severe dengue in children. This result similar with present study and statistic significantly on bivariate analysis (p=0.001, RR 3.9, CI 2.06-7.72). However from the multivariate analysis reveal unsignificantly (p= 0.87, RR 0.46, CI 0.001-291) (Table 3). Hemoglobine, and hematocrite were statistic unsignificantly (p= 0.17, RR 1.4, CI 0.75-2.6 and p= 0.74, RR 0.83 CI 0.46-1.5 respectively). The proportion of thrombocytopenia, leukopeni, hemoglobine and increase of hematocrit were 70.3%, 40.7%, 62.9% and 62.9% in severe dengue group. While in non severe dengue group the proportion were 15%, 72.5%, 50% and 70% respectively (Table. 2). Otherwise, Leukopeni was common in non severe dengue group.

Ho *et al* was reported the most notable laboratory finding included thrombocytopenia, leukopeni, prolonged APTT and elevation of serum aminotransferase.[25] According to WHO, leukopeni is common in early phase of fever.[25] Ledika *at al* in cross sectional study reported leukocyte ≥5000/mm^3 in early admission associated to severe dengue in children.[13] Pongpan *at el* was also reported white cell count > 5000/µL as prognostic factor in severe dengue.[10]

Hepatomegaly in this study was 92.6% in severe dengue group and statistic significantly in bivariate (RR 37.18, 95% CI: 3.6-352) and multivariate analysis (RR 1.97, 95% CI = 3.1-47.2). This was similar to the previous study by Jagadiskumar, held in 110 children with dengue viral infection accompanied with liver involvement reported hepatomegaly was 79%[26] and the most common symptom while Roy *et al* 2013 reported 120 subjects with dengue virus infection and proportion of liver involvement was 80.8%.[27] Enlargement of the liver (hepatomegaly) is observed at some stage of the illness in 90%-98% of children. The frequency varies with time and/or the observer.[29] Several study reported hepatomegaly > 2 cm in *defervescence* phase as prognostic factor severe dengue in children.[12,13] Pongpan was reported in dengue severity score, hepatomegaly had the highest score of predictive severe dengue in children (OR 12.31, 95% CI = 8.84–17.15, P<0.001) than other variable e.x hematocrit, age>6 years, platelets Ý50000 µL, WBC>5000µL and systolic blood pressure <90 mmHg.[10]

Liver dysfunction is one of the atypical forms of clinical manifestation in the dengue infection. Hepatomegaly is one of liver involvement in dengue infection and most commonly in children than adult patients. Clinical evidence of liver involvement in dengue infections includes the presence of hepatomegaly and increased serum liver enzymes.[28] Hepatomegaly is frequent and more common in patients with Dengue with shock than in those with DF.[29] Currently, the exact mechanism by which the host immunity damages liver is unknown. In a recent report, liver from fatal cases of dengue hemorrhagic fever (DHF) exhibited high expression of TLR2, TLR3, IL6, and granzyme B also presented iNOS, IL18, and TGFβ in inflammatory infiltrate, indicating their possible involvement in the physiopathology.[30] However Ferreira *et al* was reported CXCL10/IP10 elevation was associated with painful hepatomegaly, and both IL10 and CXCL10/IP10 were associated with liver disorders in children.[31]

In this study, Hipoalbuminemia was defined if albumin level <3.5 g/dL. Hipoalbuminemia in severe dengue group was 66.7% and 12.5% in non severe dengue group. Twelve (12 patients) with hipoalbuminemia and history of shock and 5 patients with liver involvement.

Bivariate analysis revealed statistic significantly (p=0.001, RR 3.8, CI 2.05-7.21), on the contrary, multivariate regression revealed unsignificantly (p=0.22, RR3.5, CI 0.47-26.54). Hipoproteinemia can be found in critical phase and correlated with plasma leakage. Previous study by Suwarto *et al* in adult patients was reported the lowest albumin concentration at the critical phase was ≤ 3.49 g/dL.[32] According to WHO, hypoproteinemia/ albuminaemia was a common finding as a consequence of plasma leakage in critical phase. A significantly decreased serum albumin >0.5 gm/dl from baseline or <3.5 gm % is indirect evidence of plasma leakage.[29] The serum albumin level was lower in the serious group based on Pone *et al*[33] and Elling *et al*.[34] Pone *et al* used cutoff albumin level < 3 g/dL and serious dengue disease was defined as occurrence of death, or the use amines, inotrop, colloids, mechanical ventilation, non invasive mechanical ventilation or hemodialisis.[34] Ferreira *et al* was found involvement of inflammatory cytokine CXCL10/ IP10 and IL10 in plasma leakage was shown since hypoalbuminemia was associated with both factor levels. Pleural and pericardial effusions and ascites were detected frequently in more severe patients.[31] In present study, pleural effusion more common in severe dengue (85%) than in non severe dengue group 32.5% with *chi square* revealed statistic significantly (p=0.001, RR 4.95, CI 1.9-12.7, Table 2.) even though unsignificantly based on multivariate analysis.

This study was showed that increase of APTT in severe dengue more than non-severe dengue group with proportion are 88.9%. Increasing of APTT range from 1.5x until more than 100

Table 2. Prognostic Factors based on Bivariate Analysis

Prognostic factors	Groups		P value	RR	95% CI
	Severe Dengue n 27 (%)	Non Severe Dengue n 40(%)			
Abdominal pain	23 (85)	18 (45)	**0.002***	3.6	1.4-9.3
Nausea	24 (88.9)	28 (70)	0.13	0.788	0.62-1.0
Vomiting	18(66.7)	18 (45)	0.13	1.72	0.98-3.26
Epistaxis	3 (11.1)	7(17.5)	0.71	0.71	0.69-2.54
Melena	4 (14.8)	1 (2.5)	0.16	2.16	1.25-3.7
Hematemesis	2 (7.4)	1 (2.5)	0.73	1.7	0.7-4.0
Ptechie	18 (66.7)	14 (35)	**0.022***	**2.17**	**1.15-4.15**
Rumple Leede	26 (96.2)	40 (100)	0.84	0.39	0.29-0.53
Pleural effusion	23 (85)	13 (32.5)	**<0,001***	4.95	1.9-12.7
Hepatomegaly	25 (92.6)	9 (22.5)	**<0,001***	12.1	3.1-47.2
Hemoglobin	17 (62.90	20 (50)	0.13	1.4	0.75-2.6
Leukopeni (<5000/mm^3)	11 (40.7)	29 (72.5)	**0.019***	1.7	1.09-2.9
Increase of Hematocrit	17 (62.9)	28 (70)	0.74	0.83	0.46-1.5
Thrombocytopenia (Ý50.000/µL)	19 (70.3)	6 (15)	**<0,001***	3.9	2.06-7.72
Hypoalbuminemia (< 3.5 g/dL)	18 (66.7)	5 (12.5)	**<0,001***	3.8	2.05-7.21
AST > 3x	20 (74)	16 (40)	**0.013***	2.46	1.2-5.03
ALT >3x	15 (55.6)	23 (57.5)	0.87	0.9	0.53-1.7
Increase of PPT	7 (25.9)	2 (5)	**0.036***	2.27	1.4-3.7
Increase of APT	24 (88.9)	12 (30)	**<0,001***	6.9	2.3-20.6
Secondary Dengue infection	8 (29.6)	14 (3.5)	0.64	1.18	0.58-2.4
Transfusion	9 (33.3)	0(0)	**<0,001***	3.2	2.19-4.7

* p significantly <0.05*****,*Chi square*test

Table 3. Prognostics Factors based on Multivariate Analysis

Prognostic factors	B	p	RR	95% CI
Hepatomegaly	2.77	**0.01***	69.4	2.18-287.4
Increase of APTT	3.42	**0.005***	43.25	2.6-699
Obesity/*Overweight*	4.5.3	**0,003***	94	4.47-1989
Vomiting	2.59	**0.02***	13.3	1.5-118.8
Leucopenia	-29.95	0.9	000	0.000
AST >3x			0.000	
Abdominal pain	2.87	0.27	17.68	0.09-3221
Melena	-2.65	0.14	0.071	0.002-2.28
Albumin <3.5g/dL	1.26	0.22	3.5	0.47-26.54
Pleural effusion	-0.56	0.72	0.57	0.028-11.73
Increase of PPT	-1.6	0.25	4.9	0.3-77.3
Transfusion	30.09	1	0.99	~
Hb	-1.34	0.42	0.26	0.009-7.23
Ptechie	2.27	0.16	9.7	0.42-226
Vomiting	-2.36	0.31	0.095	0.001-8.81
Thrombocytopenia(Ý 50.000/µL)	-7.8	0.81	0.46	0.001-291
Constant	-6.95	**0.001***	0.001	

* p significantly <0.05*,*Chi square*test

seconds from the normal level. Twenty patients (72.2%) with APTT elevation acompanied with hepatomegaly. *Chi-square* analysis revealed statistic significantly (RR 6.9 95% CI 2.3-20.6) (Table 2) and also multivariate analysis carried out with logistic regression as prognostic factor of severe dengue in children (RR 43.25, 95% CI: 2.6-699) (Table 3). Its similar to study held by Mishra *et al*, rise in APTT/PT also depicts severity of disease.[19]

Patients with severe dengue may have coagulation abnormalities, but these are usually not sufficient to cause major bleeding. When major bleeding does occur, it is almost always associated with profound shock since this, in combination with thrombocytopaenia, hypoxia and acidosis, can lead to multiple organ failure and advanced disseminated intravascular coagulation.[1] Prolongation of APTT in acute phase correlates with the severity of infection and can be made as early indicator DSS/DHF.[35] Plasma leakage in dengue patients also directly related to APTT level.[36] Previously, Budastra *et al* found that there was significant relationship between prolonged APTT during early stages of DHF with bleeding manifestation at the later stage of disease.[37] Coagulophaty can be induced by hepatitis viral infection due to decreasing of coagulation factors. This can be caused by either down regulation of the synthesis of specific factors or by increased consumption of specific factors. An analysis of the linear correlation and regression between the levels of aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) and APTT shows a strong association between AST/ALT elevation and APTT prolongation in DHF patients. Dysfunction of the damaged liver might be responsible for the decreased synthesis of specific factors in the intrinsic pathway.[35] In this study, increased of APTT also accompanied with AST elevation (72.2%) and ALT elevation (44.4%). While from bivariate analysis was significantly, however from multivariate logistic regression insignificantly.

Another hypothesis of coagulopathy is NS-1 protein excreted during early stage infection will binding to prothrombin may inhibit its activation.[36] Chuang *et al* was suggested that molecular mimicry between DENV and coagulation factors can induce the production of

auto antibodies with biological effects similar to those of antithrombin antibodi/ATAs found in dengue patients. These coagulation-factor cross-reactive anti-DENV antibodies can interfere with the balance of coagulation and fibrinolysis.[38]

In this presents study, elevation AST>3x in severe dengue groups and non severe dengue group were 74% and 40% respectively. Both of elevation of ALT >3x found in severe and non severe dengue groups (55.6% and 57.5%). World Health Organization defined AST or ALT 1000 units/liter (U/L) as a severe dengue.[1] Roy *et al* was reported liver dysfunction more common in subjects accompanied with warning sign. Elevation of ALT 84.4% and AST 93.7% in group with warning sign also elevation of ALT 94.5% and AST 95.5% in severe dengue group.[26] While Lee *at al* reported AST and ALT elevation might not distinguish from severe dengue with non severe dengue infection.[39] However Fernando *et al* reported liver function tests done at earlier dates might not reflect the extent of of liver involvement in acute dengue infection. The highest AST level were seen on day 6 of illness and both AST level were significantly higher in severe dengue patients.[40] In this study AST and ALT were performed in 48 hours in early admission suggest the result were statistic unsignificantly.

The limitations of this study are width confidence interval due to sample limitation. This condition caused by dengue infection commonly occurred in rainy season and rarely to be found in other season so that impacted small number subjects obtained. Outbreaks of dengue disease often occur in most tropical countries around the world, with close to 75% of the global population exposed to the disease living in the Asia-Pacific region.[41] In most disease endemic areas dengue transmission has a definite seasonality, but the reasons for the seasonal patterns are not fully understood. The amount of rainfall is the single most important factor for dengue virus transmission, since this condition is most suitable for mosquitoes to lay their eggs and for the humans and mosquito to come into contact.[42] This study was conducted with cohort observational which fever ≥ 3 days as inclusion criteria hence subjects came with various phase of illness.

CONCLUSION

In conclusion, overweight/obesity, vomiting, hepatomegaly, and prolonged APTT were prognostic factors in severe dengue infection in children. Considering these factors for awareness of Severe dengue in patients with dengue virus infection. Clinicians should emphasize the monitoring of these factors for early detection of serious dengue state.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest for this research.

REFERENCES

1. WHO. Dengue, guidelines for diagnosis, treatment, prevention and control. Genewa. 2009:1-160.
2. Karyanti MR, Kusriastuti R, Hadinegoro SR, Rovers MM, Heesterbeek H, Hoes AW, et al. The changing incidence of dengue haemorrhagic fever in Indonesia: a 45-year registry-based analysis. BMC Infect Dis. 2014;26:1-7.
3. Simons CP, Farrar JJ, Chau NV, Wills B. Dengue. N Engl J Med 2012;366:1423-32.
4. Whitehorn J, Simmons CP. The pathogenesis of dengue. Vaccine. 2011;29(42):7221-8.
5. Gutierrez G, Gresh L, Petrez MA, Elizondo D, Aviles W and Kuan G, *et al*. Evaluation of the diagnostic utility of the traditional and revised WHO dengue case definitions. Plos Negl Trop Dis. 2013;7:e2385.
6. John DV, Lin YS, Guey Perng GC. Biomarkers of severe dengue disease – a review. J Biomed Sci. 2015;22:83
7. Nguyen MT, Nguyen VV, Nguyen TH, Ho TN, Ha MT and Ta VT , *et al*. An evidence-based algorithm for early prognosis of severe dengue in the outpatient setting. Clin Infect Dis. 2017 Mar 1;64(5):656-63.

8. Potts JA, Gibbon RV, Rothman AL, Srikiatkhachorn A, Thomas SJ, Supradish PO *et al*. Prediction of dengue disease severity among pediatric Thai patients using early clinical laboratory indicators. Plos One Negl Trop Dis. 2010 August 3;4(8):e769.
9. Tuan NM, Nhan HT Chau NV, Hung NT, Tuan HM, Tram TV, *et al*. Sensitivity and specificity of a novel classifier for the early diagnosis of dengue. Plos Negl Trop Dis. 2015 Apr 2; 9(4):e0003638.
10. Pongpan S, Wisitong A, Tawichasri C, Patumond J, Namwongprom S. Development of Dengue Infection Severity Score. ISRN Pediatrics, 2013;2(1):12-8.
11. Marón GM, Clará W, Diddle JW, Pleités EB, Miller L, Macdonald G, Adderson EE. *et al*. Association between Nutritional Status and Severity of Dengue Infection in Children in El Salvador. Am J Trop Med Hyg. 2010 Feb ;82(2):324–9
12. Yulianto A, Laksono IS, Juffri M. Faktor prognosis derajat keparahan infeksi dengue. Sari Pediatri. 2016;18(3):198-203.
13. Ledika MA, Setiabudi D, Dhamayanti M. Association between clinical profiles and severe dengue iInfection in children in developing country. American Journal Epidemiology and Infectious Disease. 2015;3(3):45-9.
14. Trang NTHT, Long NP, Hue TTM, Hung LP, Trung TD , Dinh DN, *et al.* Association between nutritional status and dengue infection: a systematic review and meta-analysis. BMC Infec Dis. 2016 Apr 20;16:172.
15. Zulkipli MS, Dahlui M, Jamil N, Wai HVC, Bulgiba A, Rampai S, *et al*.The association between obesity and dengue severity among pediatric patients: A systematic review and metanalysis. Plos Negl Trop Dis. 2018 Feb 7;12(2):1-22.
16. Tan VPK, Ngim CF, Lee EZ, Ramadas A, Pong LY , Hassan SY, *et al*. The association between obesity and dengue virus (DENV) infection in hospitalised patients. Plos One. 2018 Jul 17; 13(7): e0200698.
w18. Prathyusha CV, Rao MS, Sudarsini P, Rao KUM. Clinico-haematological profile and outcome of dengue fever in children. Int J Curr Microbiol App Sci. 2013;2(10):338-46.
19. Mishra S, Ramanathan R, Agarwalla S. Clinical Profile of Dengue Fever in Children: A Study from Southern Odisha, India. Scientifica. 2016:1-6.
20. Vuong NL, Manh DH, Mai NT, Phuc LH, Luong VT, Quan VD *et al*. Criteria of "persistent vomiting" in the WHO 2009 warning signs for dengue case classification. 2016;44:14
21. Zhang H, Zou YP, Peng HJ, Zhang XH, Zhou FY, Liu ZH, Chen GX. Predictive symptoms and signs of severe dengue disease for patients with dengue fever: a meta-analysis. Biomed Research Int. 2014 July1;1-10.
22. Gupta BK, Nehera HR, Parmar S, Meena SL, Gajraj S *et al*. Acute abdomen presentation in dengue fever during recent outbreak. J acute Disease. 2017;6(5):198-204.
23. Sabbir B, Qadir H, Shafi F, Mahboob F. Acute abdominal pain in Dengue Fever. PJMHS. 2012;6:155-8.
24. Branco MD, Luna EJ, Braga Junior LL, Oliviera RV, Rios LT, Silva MD *et al.* Risk factors associated with death in Brazilian children with severe dengue: a case-control study. Clinics. 2014;69(1):55-60.
25. Ho TS, Wang SM, Lin YS, Liu CC. Clinical and predictive markers for acute for dengue infection. J Biomed Science. 2013;20:75.
26. Jagadishkumar K; Jain P, Manjunath VG, Umesh L. Hepatic involvement in dengue fever in children. Iran J Pediatr. 2011; 22(2):231-6.
27. Roy A, Sarkar D, Chakraborty S, Chaudhuri J, Ghosh P, Chakraborty S. Profile of hepatic involvement by dengue virus in dengue infected children. N Am J Med Sci. 2013; 5(8):480-5.
28. Samanta J, Sharma V. Dengue and its effect in liver. World J Clin Cases. 2016 Feb 16;3(2):125-31.
29. WHO. Comprehensive guideline for prevention dan control dengue and dengue hemorrhagic fever. New Delhi: WHO, 2011.pp.1-212.
30. Pagliari C, Quaresma JA, Fernandes ER., Stegun FW, Brasil RA, de Andrade Jr HF, *et al*. Immunopathogenesis of dengue hemorrhagic fever: contribution to the study of human liver lesions. J. Med. Virol. 2014;86:1193–7.
31. Ferreira RA, de Oliveira SA, Gandini M *et al*. Circulating cytokines and chemokines associated with plasma leakage and hepatic dysfunction in Brazilian children with dengue fever. Acta Trop. 2015;149:138-47.
32. Suwarto S, Nainggolan L, Sinto R, Effendi B, Ibrahim E, Suryamin M, R. Sasmono T. Dengue score: a proposed diagnostic predictor for pleural effusion and/or ascites in adults with dengue infection. BMC Infectious Diseases (2016) 16:322.
33. Pone SH, Hokerberg YHM, De Oliviera R, Daumas RP, Pone TM, da Silva Pone MV, Brasil P, *et al.* Clinical and laboratory signs associated to serious dengue disease in hospitalized childre. J Pediatr (Rio J). 2016;92(5):464-471.
34. Elling R, Henneke P, Hatz C, Hufnagal M. Dengue fever in children: where are we now? Pediatr Infect Dis J. 2013;32:1020-2.
35. Lei HY, Huang KJ, Lin YS, Liu HS, Liu CC. Immunopathogenesis of dengue hemorrhagic fever. Am J Infect Dis. 2008;4:1-9.
36. Chuang YC, Lin YS, Liu CC, *et al*. Factors contributing to the disturbance of coagulation and fibrinolysis in dengue virus infection. J Formos Med Assoc. 2012;112(1):12-7.
37. Budastra IN, Arhana BNP, Mudita IB. Plasma prothrombin time and activated partial thromboplastin time as predictors of bleeding manifestation during dengue hemorrhagic fever. Paediatr Indones. 2009;49(2):69-74.
38. Chuang YC, Lin YS, Liu HS, Yeh TM. Molecular Mimicry between Dengue Virus and Coagulation

Factors Induces Antibodies To Inhibit Thrombin Activity and Enhance Fibrinolysis. J Virol. 2014 ;88(23): 13759–68.
39. Lee LK, Gan VC, Lee VJ, Tan AS, Leo YS, Lye DC *et al*. Clinical relevance and discriminatory value of elevated liver aminotransferase levels for dengue severity. Plos One. 20126(6):1676.
40. Fernando S, Wijewickrama A, Gomes L, Punchihewa CT, Madusanka SD, Dissanayake H, *et al*. Patterns and causes of liver involvement in acute dengue infection. BMC Infect Dis. 2016 16:319.
41. World Health Organization, Global strategy for dengue prevention and control 2012-2020. Geneva, Switzerland, 2012
42. Chanprasopcha P, Pongsumpu P, Ming Tang I. Effect of Rainfall for the Dynamical Transmission Model of the Dengue Disease in Thailand. Comput Math Methods in Med. 2017 August 8:1-17