Predictor of Dengue Shock Syndrome Among Pediatric Dengue Infection in Limited Resource Setting

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Abstract
Introduction*: Indonesia has the most dengue outbreaks in the ASEAN region. Lack of diagnostic modality and poor sanitation especially in rural area hinders proper and prompt management of Dengue Fever.*
Aim*: Finding the early, simple, and reliable predictor of Dengue Shock Syndrome (DSS) in Indonesia.*
Materials and Methods*: A retrospective study reviewing the medical record of pediatric patient with dengue infection from 1 January 2016 to 31 March 2016 were conducted. Age, gender, dengue signs, and simple laboratory result were collected. The data acquired were then analyzed using logistic regression for multivariate analysis (P<0,05) to find the severity predictor.*
Results*: 80 cases of dengue infection were included, mean age was 7,7 ± 3.4 years old, the average length of hospital stay was 4.59 days. 28.75% of patients had DSS. From the multivariate analysis, it is found that lethargy (p= 0.00; OR 21.23), bleeding (p= 0.01; OR 0,04), cold extremities (p=0.00;OR=22.35), and increased haematocrit level (p=0.01;OR=4.72) has significant relationship with DSS while other indicator did not.*
Conclusion*: Patients presenting with lethargy, cold extremities, and increase in haematocrit level should be treated promptly and intensively as they are more likely to develop DSS compared to patients who did not.*
Keywords*: dengue, dengue severy predictor, dengue in pediatrics.*

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Tanda Awalan Infeksi Dengue pada Pasien Pediatri untuk Memprediksi Dengue Shock Syndrome di Daerah dengan Modalitas Pemeriksaan Terbatas

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Abstrak

Pendahuluan*: Indonesia memiliki jumlah* outbreak *dengue terbesar di daerah ASEAN. Kurangnya modalitas diagnosis dan sanitasi terutama di daerah terpencil menjadi faktor utama yang mempersulit penanganan segera dan tepat untuk demam dengue.*

Tujuan: *Menemukan tanda awal, sederhana, dan reliabel untuk memprediksi* Dengue Shock Syndrome *(DSS) di Indonesia.*

Metode: *Dilakukan sebuah studi retrospektif melihat rekam medis pasien pediatri dengan infeksi dengue antara 1 Januari 2016 hingga 31 Maret 2016. Umur, jenis kelamin, tanda awalan, dan hasil laboratorium sederhana dicatat. Data yang didapat kemudian dianalisis menggunakan uji regresi logistik untuk analisis multivariat (P<0,05) untuk menemukan tanda yang dapat memprediksi keparahan.*

Hasil: *Sebanyak 80 kasus sampel dengan rata-rata umur adalah 7,7 ± 3.4 tahun, lama rawat inap 4.59 hari, dan sebanyak 28.75% pasien mengalami DSS. Dari analisis multivariat didapatkan bahwa letargi (p= 0.00; OR 21.23), anggota gerak dingin (p=0.00;OR=22.35), perdarahan(p= 0.01; OR 0,04), dan peningkatan hematocrit(p=0.01;OR=4.72) memiliki hubungan yang signifikan dengan DSS. Indikator lain tidak berhubungan secara signifikan dengan DSS.*

Kesimpulan*: Pasien yang datang dengan letargi, perdarahan, dan peningkatan hematokrit perlu diberikan penanganan segera dan intensif karena berkemungkinan mengalami DSS menjadi lebih besar dibanding yang tidak memiliki tanda tersebut.*

Kata Kunci*: dengue, prediksi DSS, pediatri*

Introduction

Dengue is an arthropod-borne virus which has been long believed to come from genus Flaviviridae with four serotypes: from DENV-1 until DENV-4 but new studies have found new dengue serotypes is DENV-5, with its main host is human.[1,2] Dengue fever incidence has been on the rise in recent decades. While the exact numbers are underreported, an estimated 3.9 billion people are at risk of infection annually. Reported cases exceed 100 million with 25.000 deaths annually. Main contributors of those numbers are from tropical and sub-tropical countries including Indonesia.[3,4] In Indonesia, the Health Ministry has reported that the number of dengue outbreaks in Indonesia was the largest in ASEAN region and there is a significant rise in dengue cases from 58 in 1968 to 158.192 cases in 2009.[5]

The considerable incidence is partly if not mostly, caused by the lack of equal distribution of healthcare in Indonesia. In a rural area such as Sampang, a small city in Madura island, the diagnostic modality for Dengue is limited to only simple laboratory tests and clinical observation. Other advanced and sophisticated examinations such as NS1, Ultrasonography, Blood Gas Assay, and X-ray are either very limited or unavailable.

Moreover, low level of education and lack of health knowledge amongst the population also contributed to the difficulty of diagnosis because most of the patient presenting at the outpatient clinic is already at a higher grade of Dengue Fever. Record by the lo-

cal health department showed that Sampang had an increasing dengue fever incidence over the last four years. From 271 in 2012 up to 639 in 2015.[6] Such events lead to significant morbidity and mortality.

Although most of the dengue cases are asymptomatic and self-limiting, without proper anticipation and early diagnosis, Dengue could rapidly develop into Dengue Shock Syndrome (DSS). This condition potentially leads to significant morbidity and mortality.[7] Despite the similar studies available which assess severity predictor of dengue fever, dengue fever is known to vary widely between countries because different population which undertook the disease (particular host genetics are associated with increased susceptibility to certain infections) and different dengue serotype that commonly infect the local populace.[8–11] Moreover, there is lack of studies available in Indonesia regarding the matter. With an established early predictor in DSS, clinicians may give appropriate treatment beforehand, hindering the disease's progression and its ability to cause death.[12]

The potential mortality that it may cause without prompt treatment, the significant number of incidence in Indonesia, and the lack of studies available regarding the topic in Indonesia summed the importance of this study to treat dengue patient better. Therefore, this study aims to find the essential dengue signs and simple laboratory test's values that can be used as a predictor of dengue fever's progression into DSS. We hope this study's result can be used as an early, simple, and reliable predictor of dengue shock syndrome, especially in limited resources setting.

Materials and Methods

This is a retrospective cross-sectional study reviewing the medical record of pediatric patient with dengue infection from 1 January 2016 to 31 March 2016 in Sampang General Hospital. In Sampang general hospital, maximum age for patients to be admitted to the pediatric ward is 14 years old. Data that were collected are basic demographic data (age and gender), diagnosis (Dengue Infection Severity and DSS or non-DSS), dengue symptom, and simple laboratory results (hematocrit, white blood cell (WBC) count, and platelet count). The 'dengue symptom' assessed in this study are based on the warning signs elaborated by WHO 2009 (Abdominal pain, vomiting with low intake, lethargy, bleeding sign, and decrease in urine production) and other important signs of dengue fever (cold extremity, arthralgia or myalgia, and headache).[12] Simple laboratory signs that were assessed are also based on the critical laboratory values for dengue grading.[13]

The data extracted were analyzed using SPSS version 17. Measures of frequency, mean, median, maximum and minimum value was used to summarize and describe all of the data. P value < 0.05 was accepted as significant. To find the predictor of severe dengue infection in pediatric patients, basic demographic data, simple laboratory results, and warning signs were collected as an independent variable and analyzed using logistic regression for multivariate analysis to find its relation with DSS and non-DSS group. Simple laboratory results that will be analyzed are: leucopenia (WBC < 3500), thrombocytopenia (Plt < 100.000), and High Hematocrit (Hct $> 41\%$). Basic demographic data that will be analyzed using multivariate analysis are: gender (male or female) and age (<5 years and >5 years).

Table 1. Grading Dengue Infection Severity[13]

DF/DHF	Symptoms	Laboratory
DF*	Fever with two or more of the following sign: headache, retro-orbital pain, myalgia, atralgia, plus positive tourniquet test	Leukopenia, trombositopenia, mab be present no plasma leakage
DHF I DF	sign + positive tourniquet test	Thrombocytopenia ≤100,000/ µL, hematocrit rise ≥20%
DHF II	Above sign + spontaneus bleeding	Thrombocytopenia ≤100,000/ µL, hematocrit rise ≥20%
DHF III	Above signs plus circulatory failure (weak pulse, hypotension, restlessness)	Thrombocytopenia ≤100,000/ µL, hematocrit rise ≥20%
DHF IV	Profound shock with undetectable blood pressure and pulse	Thrombocytopenia ≤100,000/ µL, hematocrit rise ≥20%

*DHF III and DHF IV consider as DSS (Dengue Shock Syndrome)

Results

A total of 80 pediatric patients with dengue infection were found. All of the necessary data were collected and analyzed. Characteristics of the patients are elaborated in Table 2. The sex group was distributed evenly between males and females, 40 patients for each gender. The mean age of the subjects were $7,7 \pm 3.4$ years old, ranging from 0.5 - 14 years old. Most of the subject was 6 years old (n= 6; 15%). To portray the severity of the dengue infection, dengue fever grades were also described in table 2. Most of the patients were diagnosed with Dengue Haemorrhagic Fever (DHF) (n= 74; 92.5%) instead of Dengue Fever (n= 6; 7.5%) and, overall, most patients were diagnosed with DHF grade II (n= 38; 47.5%). Subjects that had Dengue Shock syndrome were 23 (28.75%).

Table 2. Patient Demographic

Parameters	Value (n = 80)
Age distribution	7,7 ± 3.4 years (0.5 - 14 years)
Sex distribution	Male = 40 (50%)
	Female = 40 (50%)
Dengue Fever grades	Dengue Fever = 6 (7.5%)
	DHF Grade 1 = 13 (16.3%)
	DHF Grade 2 = 38 (47.5%)
	DHF Grade 3 = 20 (25.0%)
	DHF Grade 4 = 3 (3.8%)
Dengue Shock Syndrome	non-DSS = 57 (71.25%)
	DSS = 23 (28.75%)

Table 3. Patient's Blood Profile

Parameter	Mean (n=80)	Minimum Value (n=80)	Maximum Value (n=80)
Smallest Hct	34.35	26.6	42.3
Largest Hct	41.3	29.6	51.8
Days of Largest Hct	4.36	2	7
Initial Platelet Counts	39,853	3,650	111,000
Platelet at Discharge	99,250	44,000	280,000
Initial WBC count	4,938	1,600	14,100
Length of Hospitalization	4.59	2	8

Blood profile of dengue patient is in Sampang General hospital are elaborated in Table 3. Smallest Hematocrit (Hct) value on the patient's had a mean of 34.35% with minimum and maximum value of 26.6% and 42.3% respectively. The largest Hct value had a mean of 41.3% with a minimum and maximum value of 29.6% and 51.8% respectively. Hct reached its peak for an average of 4.36 days, minimum and maximum values are two and seven days respectively. Initial platelet count upon admission had a mean of 39,853 cells/mm^3 with minimum and maximum value of 3,650 cells/mm^3 and 111,000 cells/mm3 respectively. Platelet at discharge was much better averaging at 99,250 cells/mm^3, and minimum and maximum value were 44,000 cells/mm^3 and 280,000 cells/mm^3 respectively. Meanwhile, initial WBC count averaged at 4,938 cells/mm3 with minimum and maximum value of 1,600 cells/mm^3 and 14,100 cells/mm^3 respectively. Length of Hospitalization was, on average, 4.59 days, the least was 2 days, and the longest was eight days.

Complete data of dengue's symptom frequency in dengue patient is elaborated on table 4. The percentage elaborated in the table is the percentage of patient with the symptom among DSS/non-DSS patient divided by those without the symptom among DSS/non-DSS patient. From the data acquired, the most common sign among all pediatric dengue patients was vomiting and low intake (n= 53; 66,25%) and abdominal pain (n= 41; 51,25%). Meanwhile, among DSS patient, the most common symptom was lethargy (n= 15; 65,21%) and vomiting (n=10; 43,74%). Other presenting signs were uncommon among DSS patient (less than 50%). Among non-DSS patients, the most common symptom was vomiting and low intake in 43(75,43%) patients. From this research, we also found that most patients do not present with any cold extremities. Cold extremities only happen in 7 out of 80 patients (8,8%) but the symp-

Table 4. Dengue's Sign and Symptom Frequency

	Signs and Symptom	Frequency (percentage) Among DSS Patient	Among non-DSS Patient	p Value	Odds Ratio	95% CI Lower	Upper
Demographic	Age (<5 years)	1 (4,34%)	14 (24,56%)	0,07	0,14	0,26	1,91
	Gender (Male)	10 (43,47%)	30 (52,63%)	0,49	0,70	0,02	1,14
	Vomiting and Low Intake	10 (43,47%)	43 (75,43%)	0,74	0,58	0,02	14,94
	Abdominal Pain	7 (30,43%)	34 (59,64%)	0,79	1,53	0,07	33,90
	Lethargy	15 (65,21%)	4 (7,01%)	0,00*	21,33	6,89	66,08
	Bleeding	6 (26,08%)	46 (80,7%)	0,01*	0,04	0,00	0,39
Symptom	Cold Extremities	6 (26,08%)	1 (1,75%)	0,00*	22,35	7,97	25,05
	Arthralgia	1 (4,34%)	7 (12,28%)	0,64	2,44	0,06	101,84
	Headache	4 (17,39%)	16 (28,07%)	0,25	5,79	0,29	116,66
	Decreased Urine Production	0 (0%)	2 (3,51%)	1,00	0,00	0,00	0,00
Lab Result	Severe Thrombocytopenia (<50.000)	18 (78,26%)	27 (47%)	0,28	1,99	0,57	6,88
	Leucopenia (<3.500)	3 (13,04%)	25 (43,85%)	0,09	0,29	0,07	1,19
	High Hematocrit (>41%)	18 (78,26%)	21 (36,84%)	0,01*	4,72	1,46	15,27

* = significantly related to DSS (p< 0,05)

tom manifested mostly in DSS patient (n=6; 26,08%) compared to non-DSS patients (n= 1; 1,75%).

From the multivariate analysis with confidence interval of 95%, we divide all the factors into 3 major group: demographic, symptom, and laboratory result. Demographic group were divided into aged below 5 years old (p=0.07;OR=0.14) and gender (p=0.49; OR=0.07), no significancy with DSS were found in this group. Vomiting and low intake (p=0.79; OR=0.58), abdominal pain (p=0.79; OR=1.53), lethargy(p=0.00; OR=21.23), bleeding (p=0.01; OR=0.04), cold extremities (p=0.00; OR=22.35), arthralgia (p=0.64; OR=2.44), headache (p=0.25; OR=5.79), and decreased urine production (p=0.00; OR=0.00) were inside symptom's group. We found that lethargy, cold extremities, and bleeding was significantly related to DSS. It is also important to note that by reading the OR, lethargy and cold extremities can be used as the predictor of DSS because its OR is higher than one. Meanwhile, bleeding is a predictor of non-DSS because its OR is less than one.

The laboratory result composed of severe thrombocytopenia (p=0.28; OR=1.99), leucopenia (p=0.09; OR=0.29), and high hematocrit (p=0.01; OR=4.72). Based on this data we found that high haematocrit was significant as DSS predictor.

Discussion

This study found that there is an equal amount of male and female infected by dengue. This record portrayed the similar possibility of both gender for being infected by dengue. Such finding is similar to the result of a study by Anker M et al.14 The study assessed male-female differences in the number of reported incident dengue fever cases in six Asian countries over ten years. For pediatric patients (aged less than 14), they found the inconsistent difference and small differences for both genders on 5 out of 6 countries studied. The result is also not surprising because Aedes aegypti, the dengue virus primary vector, are active during the daytime and pediatric patients tend to have similar activities during the day between both sexes which is going to school. Therefore, exposing both genders on a similar risk of being infected by dengue.

The majority of pediatric patients in Sampang General Hospital are either DHF grade 2 (47.5%) or grade 3 (20%). Severity in dengue cases in pediatric patients is typical because they have less capability to compensate for plasma leakage compared to adults.12 From comparing the subject's age, we found that the majority of pediatric dengue patient was 6-7 years old (n=23; 28.1%). Other studies also find a similar result: most severe dengue infection were found in the age range of 5-9 years old.[15]

Each country or specific area commonly accentuated different parameter, because the manifestation of dengue itself varied and is associated with host-agent-environment triad which differs in every region.[8–11,16] Other studies have found that pregnancy,[17] two extremes of age,[15,18] secondary infection,[19] nutrition status,[20] and presence of diabetes or hypertension in adults as risk factors for more severe dengue diseases.[21] Compared to this study, pregnancy, extremes of age, and the presence of diabetes or hypertension are irrelevant because this study focuses on the pediatric patient which mostly are not affected by those factors. Nutrition status and secondary infection can be assessed, but the data is not available on the medical record in this study.

Further study on the pediatric patient should include those data whenever possible. In Singapore, they used clinical bleeding, low serum protein, high serum urea, and low lymphocyte proportion as an indicator for progression to DHF but this is applied to adult patients only.[22,23]

Similar to this study, the authors identified two other similar kinds of research that also assessed the dengue signs that are related to the outcome of pediatric patients. Phuong et al. in 2004 assessed 700 pediatric patients in Vietnam. The study found gastrointestinal symptom, hepatomegaly and rise in hematocrit until more than 50% was a predictive sign of DSS. The result differed from this research's result. This phenomenon can be caused by a difference in population, dengue serotype, and environment. Potts JA et al24 assessed 1348 pediatric patients in Thailand and found that WBC count, monocyte percentage, hematocrit, and platelet count for identifying severe cases of Dengue with 97% sensitivity but only 48% specificity. The result of this study showed that the signs that significantly relate to DSS are lethargy, bleeding, cold extrimities, and increase haematocrite level which differed from the two similar studies which may be caused due to the difference host-agent-environment triad as mentioned previously.

This study would help to enlighten the problem of predicting DSS among pediatric dengue patient but predicting the outcome of dengue infection remains a challenge. Further studies are necessary especially those that could cover the limitation of this study. We hope this preliminary result could help in early diagnosis, timely treatment, and prevention of deaths in pediatric dengue patient.

Conclusion

Dengue infection is common in children especially around the age of 7 years old with a similar incidence

between males and females. Vomiting and low intake is the most common dengue sign amongst overall dengue patient and also amongst non-DSS patients. Dengue signs of lethargy, cold extremities, and increase in haematocrit level were significant in predicting dengue shock syndrome in the pediatric patient.

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