Characteristics of patients with dengue hemorrhagic fever and its relationship with the prevalence of dengue shock syndrome in children

Características de los pacientes con dengue hemorrágico y su relación con la prevalencia del síndrome de choque por dengue en niños

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SUMMARY

Introduction: *Many Dengue Hemorrhagic Fever (DHF) cases tend to increase from year to year. This study aims to determine DHF patients' characteristics and determine their relationship with the prevalence of Dengue Shock Syndrome (DSS) throughout children.*
Methods: *This was a retrospective study using secondary data from medical records at Siti Khodijah Hospital, Indonesia, from 2012 to 2016.*
Results: *Among 963 patients, most patients were in the 5-13 years group (72.4 %), balanced male and female, at good nutritional status (71.8 %), the parental education 74.7 % of high school students. The history*

of dengue fever before was 2.5 %, and those with multiple infections were 17.8 %. The lowest platelet value of 41.4 % in the range $5x10^4$-1 $x10^5$, followed by a range of $2x10^4$-$<5x10^4$ of 30.8 %, the percentage increase in hematocrit (HCT) in the range 1-10 % (41.1 %), 11-<20 % (29.9 %) and ≥20 % by 27.3 %. The discharge status was 97.7 % cured, 1.5 % died, and 0.8 % referred. The diagnosis of non-shock DHF was 83.7 % and 16.2 % DHF with shock. There were significant correlation in children's characteristics with DHF with prevalence of DSS including nutritional status (P=0.000), parental education (P=0.036), history of dengue fever (P=0.001), platelet value (P=0.000), the percent increase in HCT (P=0.000), and discharge status (P=0.000).
Conclusion: *Nutritional status, parental education, history of DHF, lowest platelet value, the percent*

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increase in hematocrit value, and the patient's discharge status were associated with the prevalence of DSS.

INTRODUCTION

The prevention of dengue infection in Indonesia has yielded satisfactory results through efforts to improve case management, vector control through mosquito breeding programs, and community mobilization to clean the environment (1). As similar with other infection such as *Helicobacter pylori*, environment was important factor in dengue infection (2). Since twenty years ago, the Ministry of Health of the Republic of Indonesia, assisted by professional organizations, has made guidelines for diagnosing and managing dengue infection so that the mortality rate of 46 % in 1968 could be reduced to <1 % in 2013. Also, by using integrated criteria of WHO 2009 and 1997, update management of Dengue Shock Syndrome in Pediatric cases can improve clinical management to reach the lower mortality until CFR <1 % (3,4). However, if we look at the disease's incidence, the number of dengue cases increases with increasing spread. This increase also occurs in other countries, especially tropical countries around the equator (5-7).

It is estimated that every year around 50 million people are infected with the dengue virus, of which 500 000 require hospitalization, and almost 90 % of inpatients are children. Southeast Asia, with a population of around 1.3 billion, is an endemic area (7). Indonesia, along with Bangladesh, India, Maldives, Myanmar, Sri Lanka, Thailand, and Timor Leste, falls into endemic A (high endemic). In that country, dengue is the main reason for hospitalization and one of the leading causes of death in children (5). Over six years, 13.940 patients were treated, consisting of 5 931 dengue fever (DF), 5 844 dengue hemorrhagic fever (DHF), and 2 165 dengue shock syndrome (DSS) patients (5). The highest age group is 5-14 years, namely 9 036 (64.8 %). The percentage of death cases of dengue infection is 0.08 % DF, 0.36 % DHF, and 7.81 % DSS (7).

The most common cause of death is in the DSS group. In addition to shock cases that cause death, it has also been reported in some cases of unusual clinical manifestations such as dengue encephalopathy, disseminated intravascular coagulation, and some cases accompanied by comorbidities such as Human Immunodeficiency Virus (HIV) infection and sepsis (8,9). Clinical manifestations of dengue virus infection are extensive can be asymptomatic/symptomatic, fever that is not typical/challenging to distinguish from other viral infections, DF, DHF, and expanded dengue syndrome/organopathy (unusual clinical manifestations). DHF itself is distinguished from dengue fever by the presence of plasma leakage and categorized with non-shock DHF and DHF with shock (DSS) (9,10).

Siti Khodijah Hospital, Sepanjang, is a type B hospital located in Sidoarjo, Indonesia. Like most hospitals in East Java, Siti Khodijah Hospital, Sepanjang, in Indonesia also treated dengue cases in the top 10 most diseases, especially in children. Data from the Siti Khodijah Hospital Medical Record recorded with dengue and dengue fever diagnosis in patients with children for five years from 2012 to 2016 tend to increase (data not shown). Seeing the number of dengue cases and the tendency to increase, this study aims to conduct initial research on DHF patients' characteristics and their relationship to the prevalence of shock in children.

METHODS

This study is retrospective, using secondary data from medical records at Siti Khodijah Hospital, Indonesia, from 2012 to 2016. The data were collected for six months from July to December 2018. Diagnosis of DHF with or without shock was taken from the medical record when the patient returns from the hospital, and this is done by the physicians who are treating the patients. Descriptive analysis was used to determine the characteristics and distribution of samples, namely percent increase in hematocrit, lowest platelet value, age, sex, nutritional status, parental education, previous history of dengue pain, multiple infections, and patient status out of the hospital. A statistical test to assess the relationship between the patient characteristics

and DSS events' prevalence was carried out using the Spearman correlation test.

RESULTS

Within five years, a total sample of pediatric patients diagnosed with DHF in the medical record of 1 015 sufferers was obtained. After the recapitulation, 52 medical records were obtained, with laboratory data not attached, so they were excluded from the study sample. So that the number of samples studied is 963. Characteristics of children with DHF are shown in Table 1. The characteristics were age, sex, nutritional status, parental education, previous history of dengue fever, multiple infections, lowest platelet value, the percent increase in hematocrit, discharge status, and patient diagnosis.

Table 1
Characteristics of Children with DHF

Patient characteristics	Category	Frequency	Percentage
Age	1 month - <1 year	59	6.1
	1 year - <5 year	207	21.5
	5 year - 13 year	697	72.4
Sex	Male	499	51.8
	Female	464	48.2
Nutritional status	Good	691	71.8
	Deficient	124	12.9
	Poor	23	2.4
	Excess	125	12.9
Parental education	Elementary school	36	3.7
	Junior high school	80	8.3
	Senior high school	719	74.7
	University	128	13.3
Previous history of dengue fever	Yes	24	2.5
	No	939	97.5
Multiple infections	Yes	24	2.5
	No	939	97.5
Lowest platelet value	$<2x10^4$	95	9.9
	$2x10^4$-$<5x10^4$	297	30.8
	$5x10^4$-$1x10^5$	399	41.4
	$>1x10^5$	172	17.9
Percent increase in hematocrit	1-10 %	396	41.1
	11-< 20 %	288	29.9
	≥20 %	263	27.3
Discharge status	Lab Exam 1x	16	1.7
	Heal	941	97.7
	Died	14	1.5
	Referred	8	0.8
Patient diagnosis	DHF without shock	806	83.7
	DSS	157	16.3

DHF: Dengue Hemorrhagic Fever

The statistical analysis of characteristics of patient's correlation with DSS genesis prevalence is shown in Table 2. Patients' characteristics with significant results were age, nutritional status, parent education, history of dengue pain, low platelet values, percentage of hemoconcentration, and patients' discharge status.

Table 2

Characteristics of patients correlation with DSS genesis prevalence

Characteristics	Correlation coefficient Spearman's rho	Sig. (2-tailed)
Age	.052	.109
Sex	-.032	.325
Nutritional status	.120**	.000
Parental education	-.068*	.036
Previous history of dengue fever	.110**	.001
Multiple infections	.043	.180
Lowest platelet value	-.202**	.000
Percent increase in hematocrit	.295**	.000
Discharge status	.290**	.000

**Correlation is significant the 0.01 level (2-tailed)
*Correlation is significant at the 0.05 level (2-tailed)

DISCUSSION

This study revealed that nutritional status, parental education, history of DHF, lowest platelet value, and the percent increase in the patient's hematocrit value and discharge status were associated with the prevalence of DSS events. The number of malnutrition found was only 22 cases (<0.01 %) of the total population in 2014 of 2 104 912 people in Sidoarjo, Indonesia (11). A 2013 meta-analysis with nine studies examined found an association between malnutrition and DSS events (OR: 1.19, 95 % CI: 1.00-1.41). This meta-analysis also conducted an analysis looking for a normal nutritional relationship with DSS, where the results obtained are the opposite relationship between normal nutritional status with DSS events (OR: 0.87, 95 % CI: 0.77-0.99) (12). Based on the same meta-analysis, eight existing studies concluded that obesity/overweight is not related to DSS incidence (OR: 1.31, 95 % CI: 0.91-1.88) (12). However, a report concluded that overweight/obesity was one of the prognostic factors in severe dengue infection in children (13). DSS is more common in immunocompetent children and good nutritional status than in immunocompromised children. Whereas in malnutrition, DSS is very rare (14). Good nutritional status is associated with a good immune response which can cause severe DHF (15). Another researcher also has the same opinion that there is no significant difference between good nutritional status and malnutrition on DSS events in children (16-18).

Moreover, it can also explain that most parents' education level was 74.7 % of senior secondary, followed by tertiary education 13.3 %, junior high school, 8.3 %, and elementary school, 3.7 %. This shows knowledge level of the most parents of DHF patients was quite good. A report also stated that parents level of knowledge plays an essential role in the behavior of prevention of DHF (19). For data on education distribution according to Regional Government Administration Report of Sidoarjo Regency, Indonesia. In 2014, even most of the tertiary education level population was 54.9 %, followed by the senior high school at 20.3 %, junior high school at 11.4 %, and elementary/equivalent 13.3 % (11). A study concluded that prevention of DHF shock might be achieved through health

education interventions in the form of counseling. It might improve parents' cognition and affection aspects (knowledge and attitude) of dengue fever in doing self-care and prevention (20).

Secondary data about the history of ever having dengue fever was found to be very small. It is said that the first infection (primary) causes lifelong immunity to the cause serotype, for secondary infections with different viral serotypes (secondary heterologous infection) generally provide more severe clinical manifestations than primary infection (5).

DSS often occurs when the platelet count $<5x10^4/mm^3$ (16,21,22). The previous study stated that a negative relationship was found in platelet counts conducted by 37 studies (12). So the lower the platelet count and the higher the hemoconcentration, especially $\geq 20\%$, contribute significantly to DSS occurrence (10). This is the basis of the diagnostic criteria for DHF diagnosis by WHO.

Hemoconcentration is defined by an increase in hematocrit $>20\%$ of the standard value based on age. Patients with hematocrit levels at admission $>42\%$ are twice as likely to experience shock than $<42\%$ (22,23). In this study, the essential diagnosis used was the diagnosis of dengue patients recorded in medical records. Thus, the stated diagnosis of the patient is the treating physician. If the diagnosis of DHF is recapitulated, but it is not supported by platelet reduction data $<1x10^5$ or hemoconcentration incidence $\geq 20\%$, then the assumption that doctors diagnose the clinical criteria for dengue fever is very likely to be biased with the diagnosis of DF (22). This is one of the weaknesses of this study, where the diagnosis was determined based on the Medical Record records that the doctor made.

Of the 14 DHF cases that died, 13 cases were diagnosed with dengue with shock, and from 8 complex cases of DHF referred to, six were diagnosed with dengue with shock. If shock occurs, the body first compensates (compensated shock). Severe bleeding that occurs causes a decrease in hematocrit, and the number of leukocytes that originally leukopenia can increase as a stress response in patients with severe bleeding. Some patients enter the critical phase of plasma permeation and then experience

shock before the fever falls, in which the increase in hematocrit and thrombocytopenia occur very quickly. Besides, in DHF patients accompanied by shock or organ involvement cannot occur, such as severe hepatitis, encephalitis, myocarditis, and/or severe bleeding. This is known as expanded dengue syndrome (5) (14).

The age range in this study is between 5 years to 13 years. The previous research stated that the age factor influences dengue infection patients to experience DSS, and it explained 17 % of DHF patients experienced DSS, and the proportion of the most significant incidence was experienced by the age group of fewer than five years (58.8 %) (24). Babies aged 6-12 months have a more severe risk, even in primary infections (5) (25). A study meta-analysis concluded that the pooling of odds ratios from several studies showed a negative relationship between age and DSS events (OR: 0.50, 95 % CI: 0.36-0.70) (12,24,26).

Sex characteristics in the sample distribution were almost the same at 51.8 % and 48.2 % female. It can be assumed that the number of males and females and the level of activities inside and outside the home was not much different. According to a previous study with multiple samples, it was concluded that the prevalence by sex did not reveal any significant differences between women and men (15,22,27). Therefore, a study meta-analysis showed that there was a significant relationship between female sex and DSS (12).

CONCLUSION

Nutritional status, parental education, history of DHF, lowest platelet value, the percent increase in hematocrit value, and the patients' discharge status were associated with the prevalence of DSS events.

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Conflicts of Interest

The authors declare no conflict of interest.

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