

CHARACTERISTICS OF PATIENTS WITH DENGUE HEMORRHAGIC FEVER AND ITS RELATIONSHIP WITH THE PREVALENCE OF DENGUE SHOCK SYNDROME IN CHILDREN

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1 **CHARACTERISTICS OF PATIENTS WITH DENGUE HEMORRHAGIC FEVER**
2 **AND ITS RELATIONSHIP WITH THE PREVALENCE OF DENGUE SHOCK**
3 **SYNDROME IN CHILDREN**

4

5 **Running Title: Relationship of DHF and DSS in Children**

6

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1 **ABSTRACT**

2 **Introduction:** Many Dengue Hemorrhagic Fever (DHF) cases tend to increase from year to
3 year. This study aims to determine DHF patients' characteristics and determine their
4 relationship with the prevalence of Dengue Shock Syndrome (DSS) throughout children.

5 **Methods:** This was a retrospective study using secondary data from medical records at Siti
6 Khodijah Hospital, Indonesia, from 2012 to 2016.

7 **Results:** Among 963 patients, most patients were in the 5-13 years group (72.4%), balanced
8 male and female, at good nutritional status (71.8%), the parental education 74.7% of high
9 school students. The history of dengue fever before was 2.5%, and those with multiple
10 infections were 17.8%. The lowest platelet value of 41.4% in the range $5 \times 10^4 - 1 \times 10^5$, followed
11 by a range of $2 \times 10^4 - < 5 \times 10^4$ of 30.8%, the percentage increase in hematocrit (HCT) in the range
12 1-10% (41.1%), 11-<20% (29.9%) and $\geq 20\%$ by 27.3%. The discharge status was 97.7% cured,
13 1.5% died, and 0.8% referred. The diagnosis of non-shock DHF was 83.7% and 16.2% DHF
14 with shock. There were significant correlation in children's characteristics with DHF with
15 prevalence of DSS including nutritional status ($p=0.000$), parental education ($p=0.036$), history
16 of dengue fever ($p=0.001$), platelet value ($p=0.000$), the percent increase in HCT ($p=0.000$),
17 and discharge status ($p=0.000$).

18 **Conclusion:** Nutritional status, parental education, history of DHF, lowest platelet value, the
19 percent increase in hematocrit value, and the patient's discharge status were associated with
20 the prevalence of DSS events.

21

22 **Keywords:** Hemorrhagic; Dengue; Shock; Syndrome; Children

1 INTRODUCTION

2 The prevention of dengue infection in Indonesia has yielded satisfactory results through
3 efforts to improve case management, vector control through mosquito breeding programs,
4 and community mobilization to clean the environment (1). Since twenty years ago, ¹¹ the
5 Ministry of Health of the Republic of Indonesia, assisted by professional organizations, has
6 made guidelines for diagnosing and managing dengue infection so that the mortality rate of
7 46% in 1968 could be reduced to <1% in 2013. Also, ¹⁰ by using integrated criteria of WHO
8 2009 and 1997, update management of Dengue Shock Syndrome in Pediatric cases can
9 improve clinical management to reach the lower mortality until CFR <1% (2,3). However, if
10 we look at the disease's incidence, the number of dengue cases increases with increasing
11 spread. This increase also occurs in other countries, especially tropical countries around the
12 equator (4-6).

13 ²⁴ It is estimated that every year around 50 million people are infected with the dengue
14 virus, of which 500.000 require hospitalization, and almost 90% of inpatients are children.
15 Southeast Asia, with a population of around 1.3 billion, is an endemic area (6). Indonesia,
16 along with ²⁷ Bangladesh, India, Maldives, Myanmar, Sri Lanka, Thailand, and Timor Leste,
17 falls into endemic A (high endemic). In that country, dengue is the main reason for
18 hospitalization and ²⁹ one of the leading causes of death in children (4). Over six years, 13.940
19 patients were treated, consisting of ²⁰ 5.931 dengue fever (DF), 5.844 dengue hemorrhagic fever
20 (DHF), and 2.165 dengue shock syndrome (DSS) patients (4). The highest age group is 5-14
21 years, namely 9.036 (64.8%). The percentage of death cases of dengue infection is 0.08% DF,
22 0.36% DHF, and 7.81% DSS (6).

23 The most common cause of death is in the DSS group. In addition to shock cases that
24 cause death, it has also been reported in some cases of unusual clinical manifestations such as
25 dengue encephalopathy, disseminated intravascular coagulation, and some cases

26 accompanied by comorbidities such as Human Immunodeficiency Virus (HIV) infection and
27 sepsis (7,8).

28 Clinical manifestations of dengue virus infection are extensive can be
29 asymptomatic/symptomatic, fever that is not typical/challenging to distinguish from other
30 viral infections, DF, DHF, and expanded dengue syndrome/organopathy (unusual clinical
31 manifestations). DHF itself is distinguished from dengue fever by the presence of plasma
32 leakage and categorized with non-shock DHF and DHF with shock (DSS) (8,9) .

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

1 **METHODS**

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

1 RESULTS

2 Within five years, a total sample of pediatric patients diagnosed with DHF in the medical
3 record of 1.015 sufferers was obtained. After the recapitulation, 52 medical records were
4 obtained, with laboratory data not attached, so they were excluded from the study sample. So
5 that the number of samples studied is 963. Characteristics of children with DHF are shown in
6 Table 1. The characteristics were age, sex, nutritional status, parental education, previous
7 history of dengue fever, multiple infections, lowest platelet value, the percent increase in
8 hematocrit, discharge status, and patient diagnosis.

9 **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 %
Parental education	Excess	125	12.9 %
	Elementary school	36	3.7 %
	Junior high school	80	8.3 %
	Senior high school	719	74.7 %
Previous history of dengue fever	University	128	13.3 %
	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%
Patient Diagnosis	Referred	8	0.8 %
	DHF without shock	806	83.7 %
	DSS	157	16.3 %

10 DHF: Dengue Hemorrhagic Fever

11

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

16 **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)*

1 **DISCUSSION**

2 This study revealed that nutritional status, parental education, history of DHF, lowest platelet
3 value, and the percent increase in the patient's hematocrit value and discharge status were
4 associated with the prevalence of DSS events. The number of malnutrition found was only 22
5 cases (<0.01%) of the total population in 2014 of 2.104.912 people in Sidoarjo, Indonesia
6 (10). A 2013 meta-analysis with nine studies examined found an ²⁵association between
7 malnutrition and DSS events (OR: 1.19, 95% CI: 1.00-1.41). This meta-analysis also
8 conducted an analysis looking for a normal nutritional relationship with DSS, where the
9 results obtained are the opposite relationship between normal nutritional status with DSS
10 events (OR: 0.87, 95% CI: 0.77-0.99) (11). Based on the same meta-analysis, eight existing
11 studies concluded that obesity/overweight is not ¹²related to DSS incidence (OR: 1.31, 95% CI:
12 0.91-1.88) (11). However, a report concluded that overweight/obesity was one of the
13 prognostic factors in severe dengue infection in children (12). DSS is more common in
14 immunocompetent children and good nutritional status than in immunocompromised
15 children. Whereas in malnutrition, DSS is very rare (13). Good nutritional status is associated
16 with a good immune response which can cause severe DHF (14). Another researcher also has
17 the same opinion that there is no significant difference between good nutritional status and
18 malnutrition on DSS events in children (15–17).

19 Moreover, it can also explain that most parents' education level was 74.7% of senior
20 secondary, followed by tertiary education 13.3%, junior high school, 8.3%, and elementary
21 school, 3.7%. This shows knowledge level of the most parents of DHF patients was quite
22 good. A report also stated that parents level of knowledge plays an essential role in the
23 behavior of prevention of DHF (18). For data on education distribution according to Regional
24 Government Administration Report of Sidoarjo Regency, Indonesia. In 2014, even most of
25 the tertiary education level population was 54.9%, followed by the senior high school at

26 20.3%, junior high school at 11.4%, and elementary/equivalent 13.3% (10). A study
27 concluded that prevention of DHF shock might be achieved through health education
28 interventions in the form of counseling. It might improve parents' cognition and affection
29 aspects (knowledge and attitude) of dengue fever in doing self-care and prevention (19).

30 Secondary data about the history of ever having dengue fever was found to be very
31 small. It is said that the first infection (primary) causes lifelong immunity to the cause
32 serotype, for secondary infections with different viral serotypes (secondary heterologous
33 infection) generally provide more severe clinical manifestations than primary infection (4).

34 DSS often occurs when the platelet count $<5 \times 10^4/\text{mm}^3$ (15,20,21). The previous study
35 stated that a negative relationship was found in platelet counts conducted by 37 studies (11).
36 So the lower the platelet count and the higher the hemoconcentration, especially $\geq 20\%$,
37 contribute significantly to DSS occurrence (9). This is the basis of the diagnostic criteria for
38 DHF diagnosis by WHO.

39 Hemoconcentration is defined by an increase in hematocrit $>20\%$ of the standard value
40 based on age. Patients with hematocrit levels at admission $>42\%$ are twice as likely to
41 experience shock than $<42\%$ (21,22). In this study, the essential diagnosis used was the
42 diagnosis of dengue patients recorded in medical records. Thus, the stated diagnosis of the
43 patient is the treating physician. If the diagnosis of DHF is recapitulated, but it is not
44 supported by platelet reduction data $<1 \times 10^5$ or hemoconcentration incidence $\geq 20\%$, then the
45 assumption that doctors diagnose the clinical criteria for dengue fever is very likely to be
46 biased with the diagnosis of DF (21). This is one of the weaknesses of this study, where the
47 diagnosis was determined based on the Medical Record records that the doctor made.

48 Of the 14 DHF cases that died, 13 cases were diagnosed with dengue with shock, and
49 from 8 complex cases of DHF referred to, six were diagnosed with dengue with shock. If
50 shock occurs, the body first compensates (compensated shock). Severe bleeding that occurs

51 causes a decrease in hematocrit, and the number of leukocytes that originally leukopenia can
52 increase as a stress response in patients with severe bleeding. Some patients enter the critical
53 phase of plasma permeation and then experience shock before the fever falls, in which the
54 increase in hematocrit and thrombocytopenia occur very quickly. Besides, in DHF patients
55 accompanied by shock or organ involvement cannot occur, such as severe hepatitis,
56 encephalitis, myocarditis, and/or severe bleeding. This is known as expanded dengue
57 syndrome (4) (13).

58 The age range in this study is between 5 years to 13 years. The previous research stated
59 that the age factor influences dengue infection patients to experience DSS, and it explained
60 17% of DHF patients experienced DSS, and the proportion of the most significant incidence
61 was experienced by the age group of fewer than five years (58.8%) (23). Babies aged 6-12
62 months have a more severe risk, even in primary infections (4) (24). A study meta-analysis
63 concluded that the pooling of odds ratios from several studies showed a ¹²negative relationship
64 between age and DSS events (OR: 0.50, 95% CI: 0.36-0.70) (11,23,25).

65 Sex characteristics in the sample distribution were almost the same at 51.8% and 48.2%
66 female. It can be assumed that the number of males and females and the level of activities
67 inside and outside the home was not much different. According to a previous study with
68 multiple samples, it was concluded that the prevalence by sex did not reveal any significant
69 differences between women and men (14,21,26). Therefore, a study meta-²³analysis showed
70 that there was a significant relationship between female sex and DSS (11).

71

1 **CONCLUSION**

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

5

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11

12 ²¹ **Conflicts of Interest**

13 The authors declare no conflict of interest.

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