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Hemoconcentration as Predictor of Dengue Hemorrhagic Fever Infection Severity in Pediatric Patients

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ABSTRACT

Background: Dengue infection can be asymptomatic or symptomatic, as undifferentiated, dengue fever or dengue hemorrhagic fever, or may even be a dengue shock syndrome. The progression of dengue hemorrhagic infections varies in each person. Patients with mild clinical symptoms may initially progress rapidly to more severe even to death. Assessment of the degree of severity as early as possible is important for adequate management, preventing shock and further bleeding. The objective of this study is to determine the association between patient characteristics, clinical symptoms, and laboratory results with the severity of infection in dengue hemorrhagic fever.

Method: This study was an observational analytic study with a prospective cohort design, sampling was done by looking at the medical record, laboratory results, and anamnesis was done by using questionnaires on the first day of hospital admission and followed during treatment until the determination of DF and DHF diagnosis. This research was conducted from May to October 2017 in the pediatric ward in Sleman and Bantul Regional Public Hospital, Yogyakarta. The subjects of this study were 42 patients consisting of 24 patients with severe dengue and 18 patients with mild dengue.

Results: The bivariate analysis found that age, gender, and length of treatment showed no significant difference in dengue severity ($p>0.05$). Clinical symptoms of fever duration, headache duration, abdominal pain, days starting nauseous, petechiae, vomiting frequency, myalgia, arthralgia, nosebleeds, and bleeding gums showed no significant difference. The laboratory result of hematocrit, and hemoconcentration during hospitalization showed a significant difference in dengue severity ($p<0.05$) whereas thrombocytopenia showed no significant difference. Multivariate analysis found hemoconcentration during hospitalization showed a significant association with dengue severity ($p<0.05$).

Conclusion: This result shows that hemoconcentration can be used as a predictor of dengue hemorrhagic fever severity of infection in pediatric patients in Sleman and Bantul Regional Public Hospital.

1. Introduction

Dengue fever is one of the most common tropical diseases in humans. Dengue fever has become a major international public health problem in recent decades. The World Health Organization (WHO) estimates that approximately 2.5 to 3 billion people currently live in dengue-affected areas (1). In the WHO Southeast Asia region, 10 out of 11 Member States are known to be endemic for dengue virus. In 2023, several countries, including Bangladesh and Thailand, have reported a notable surge in dengue

cases compared to previous years. In particular, India, Indonesia, Myanmar, Sri Lanka and Thailand rank among the world's 30 most highly endemic countries (2).

Dengue fever is an acute febrile illness caused by infection with the dengue virus (DENV). DENV is a single-stranded RNA flavivirus that is a member of the Flaviviridae family. This virus has four major serotypes (DENV-1, DENV-2, DENV-3, and DENV-4). Humans become infected with dengue through the bite of her DENV-carrying female Aedes aegypti, such as Aedes albopictus and Aedes aegypti. Subsequent infection with her specific DENV serotype is associated with an increased risk of serious complications (1).

Dengue infection can be asymptomatic or symptomatic. Clinical manifestations of dengue are characterized by sudden fever 2 to 7 days with no obvious cause, weakness/lethargy, anxiety, heartburn, a manifestation of plasma leakage, hemorrhagic bleeding (petechiae), bruising (ecchymosis) or rash (purpura), laboratory results indicating the presence of leucopenia, hematocrit, thrombocytopenia, and hemoconcentration. Sometimes nosebleeds, dysentery, vomiting, decreased awareness, or shock (3).

The manifestations of DENV infection range from mild acute undifferentiated febrile illness to classic dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS). DF is an acute febrile illness with symptoms such as bone, joint, and muscle pain, headache, leukopenia, and rash. DHF has four major clinical manifestations. Severe fever, bleeding, often with hepatomegaly, and in severe cases circulatory failure (4). Some infected people experience hypovolemic shock due to severe plasma leakage caused by DSS.

The progression of dengue hemorrhagic infections varies in each person. Patients with mild clinical symptoms may initially progress rapidly to more severe even to death. Each degree of dengue hemorrhagic fever gives a clinical symptom that we can monitor during therapy. Diagnosis as early as possible and proper assessment of the staging is a very important factors in determining patient prognosis (5).

Dengue fever is common and even more dangerous when occurs in children. Since there are no real guidelines for dealing with DHF, efforts to control the risk factors that cause DHF outbreaks in children are needed to reduce morbidity and mortality (6). Age is included in the host factor which can affect the sensitivity to viral infection from dengue fever. According to WHO in 2003, the age limit for children is 0-14 years, and for adults is over 14 years. Meanwhile, the age limit for children according to WHO in 2010 is 0-19 years, and adults are over 19 years. DHF is more common at a younger age because it has a stronger immune response than adults (7).

Therefore, assessment of the degree of severity as early as possible is important for adequate management, preventing shock and further bleeding. The objective of this study is to determine the association between patient characteristics, clinical symptoms, and laboratory results with the severity of dengue hemorrhagic fever infection in pediatric patients.

2. Method

This study was an observational analytic study with a prospective cohort design, sampling was done by looking at the medical record, laboratory results, and anamnesis was done by using questionnaires on the first day of hospital admission and followed during treatment until the determination of mild dengue) and severe dengue diagnosis by a doctor. This research was conducted from May to October 2017 in Sleman and Bantul Regional Public Hospital, Special Region of Yogyakarta. The total sample in this study was 42 pediatric patients. Dengue cases in this study were patients with dengue fever and dengue hemorrhagic fever diagnosis in Sleman and Bantul Regional Public Hospital in pediatric wards who had the inclusion and exclusion criteria as follows:

Inclusion criteria: age 0-19 years old, positive rapid diagnostic test (RDT) NS1 and/or IgM anti-dengue, admission to the hospital during fever (2-5 days), at the pediatric ward in Sleman and Bantul Regional Public Hospital, and willing to participate in research. Exclusion criteria: comorbid diagnosed with other infectious diseases such as typhoid fever, malaria, leptospirosis, hepatitis, HIV, tuberculosis; diseases of blood cell production failure such as anemia, thalassemia, immune thrombocytopenic purpura; diseases of blood clotting disorders such as hemophilia, immune diseases such as systemic

lupus erythematosus; or metabolic diseases and other organ disorders such as; diabetes mellitus, hypertension, kidney disease.

Descriptive analysis was used to analyze the distribution of patient characteristics, clinical symptoms, laboratory results, and the dengue degree. Bivariate analysis was conducted to see the relationship between the dependent variable and independent variable. Multivariate analysis was conducted to know the relation between patient characteristics, clinical symptoms, laboratory results, and the dengue degree.

3. Result

Patient Characteristic

The subjects of this study were 42 patients consisting of 24 patients with severe dengue and 18 patients with mild dengue, bivariate analysis result of patient characteristics can be seen in table 1.

Table 1. Bivariate analysis result of patient characteristics.

Patient Characteristics	Dengue Degree		p-value
	Mild Dengue	*Severe Dengue*	
Ages			0,052
* ≤ 5 years	8 (19)	4 (9,5)	
* 6 - 19 years	10 (23,8)	20 (47,6)	
Sex			0,589
* Male	10 (23,8)	13 (31)	
* Female	8 (19)	11 (26,2)	
length of treatment			0,098
* ≤ 6 days	12 (28,6)	10 (23,8)	
* > 6 days	6 (14,3)	14 (33,3)	

Based on Table 1, the most severe degree of DHF was found at the age of 6-19 years (47.6%) and male gender (31%). The average length of treatment in patients with severe dengue was 6.6 ± 0.8 days, whereas for patients with mild dengue was 6.1 ± 1.0 days. Bivariate analysis results from the patient characteristic of the age, sex, and length of treatment showed no significant difference (p>0,05).

Clinical Symptoms

Clinical symptoms have been observed during treatment, consisting of fever duration, days starting headache, abdominal pain, days starting nauseous, petechiae, vomiting frequency, myalgia, arthralgia, nosebleeds, and bleeding gums. bivariate analysis result of clinical symptoms can be seen in table 2.

Table 2. Bivariate analysis result of clinical symptoms

Clinical Symptoms	Dengue Degree		p-value
	Mild Dengue	*Severe Dengue*	
fever duration			0,665
* ≤ 3 days	3 (7,1)	4 (9,5)	
* > 3 days	15 (35,7)	20 (47,6)	
days starting headache			0,64
* 1st day	12 (30)	18 (45)	
* ≥ 2nd day	4 (10)	6 (15)	
abdominal pain			0,178
* yes	16 (38,1)	24 (57,1)	
* no	2 (4,8)	0 (0)	

Clinical Symptoms	Dengue Degree		p-value
	Mild Dengue	*Severe Dengue*	
days starting nauseous			0,175
*≤ 2nd day	11 (26,2)	10 (23,8)	
* > 2nd day	7 (16,7)	14 (33,33)	
Petechiae			0,679
* yes	17 (40,5)	23 (54,8)	
* no	1 (2,4)	1 (2,4)	
vomiting frequency			0,286
* ≤ 3 times	15 (35,7)	17 (40,5)	
* > 3 times	3 (7,1)	7 (16,7)	
Myalgia			0,178
* upper and lower extremities	16 (38,1)	24 (57,1)	
* no	2 (4,8)	0 (0)	
Arthralgia			0,178
* upper and lower extremities	16 (38,1)	24 (57,1)	
* no	2 (4,8)	0 (0)	
Nosebleeds			0,151
* yes	2 (4,8)	7 (16,7)	
* no	16 (38,1)	17 (40,5)	
bleeding gums			0,571
* yes		1 (2,4)	
* no	18 (42,9)	23 (54,8)	

Based on Table 2, majority of mild dengue have fever for more than 3 days, headache on the first day, nausea from the first/second day, abdominal pain, petechiae, more than 3 times vomiting, myalgia, arthralgia, very little nosebleed, and no bleeding gum. Severe dengue also experienced almost the same symptoms, but all 24 severe dengue patients experienced abdominal pain, myalgia, arthralgia, and no bleeding gum. Another difference in patients with severe dengue symptoms of nausea appeared before or after the second day with almost equal proportions. Bivariate analysis results from clinical symptoms of fever duration, headache duration, abdominal pain, days starting nauseous, petechiae, vomiting frequency, myalgia, arthralgia, nosebleeds, and bleeding gums showed no significant difference (p>0,05).

Laboratory Results

Laboratory results have been done and observed consisting of hematocrit, hemoconcentration, and platelet. Bivariate analysis results of laboratory results can be seen in table 3.

Table 3. Bivariate analysis result of laboratory results

Laboratory Results	Dengue Degree		p value
	Mild Dengue	*Severe Dengue*	
Hematocrit			0,004*
* ≤ 42	16 (38,1)	11 (26,2)	
* > 42	2 (4,8)	13 (31)	
Hemoconcentration			0,007*
* ≤ 15%	15 (35,7)	10 (23,8)	
* > 15%	3 (7,1)	14 (33,33)	
Platelet (mm^3)			0,233

*< 50.000	2 (4,8)	6 (14,3)
*> 50.000	16 (38,1)	18 (42,86)

*p value < 0,05

Based on Table 3, majority of mild dengue showed laboratory results of hematocrit value ≤ 42, hemoconcentration ≤ 15%, and platelet t > 50.000 (mm3). In severe dengue patients, laboratory results also showed the majority of platelet > 50,000 (mm3), but other laboratory results for hematocrit and hemoconcentration showed different results where the majority of hematocrit values> 42, hemoconcentration >15%. Bivariate analysis results from laboratory results of hematocrit and hemoconcentration showed a significant difference (p<0,05), whereas thrombocytopenia showed no significant difference (p>0,05).

Multivariate Analysis

Multivariate analysis was carried out on variables with p value < 0.1 (age, hematocrit, hemoconcentration) to determine the correlation between variables and dengue severity. Multivariate analysis result can be seen in table 4.

Table 4. Multivariate analysis result

Variabel	*Coefficient (β)*	*Standard Error (SE)*		*Exp.(B)*	*95%CI*	
					lower	upper
Age	1,747	0,96	0,069	5,735	0,873	37,675
hematocrit	1,646	0,923	0,074	5,186	0,85	31,64
hemoconcentration	1,823	0,92	0,048*	6,19	1,02	37,56
Constant	-2,111	0,957	0,027	0,121		

*p value < 0,05

Based on Table 4, hemoconcentration variables have a significant association with the severity of dengue hemorrhagic fever infection with a value of p<0,05 (0.003); OR 6,19; (95% CI: 1,02-37,56), whereas age and hematocrit variable has no significant association.

4. Discussion

In this study, case distribution of dengue fever predominantly affected children within the age group of 6-19 years rather than those aged 0-5 years. Several factors contribute to this disparity. Children above five years old typically spend more time outdoors, increasing their exposure to mosquito vectors carrying the virus. This heightened exposure risk likely contributes to the higher incidence rate in older children (8,9). School-aged children engage in activities that bring them closer to potential breeding sites of mosquitoes, such as playing near standing water areas. Additionally, their daily routines involve interactions with peers, further amplifying social contact networks that facilitate transmission.

Another finding on this study shows severe dengue degrees are highest at the age of 6-19 years. Younger children often lack sufficient immunity against dengue viruses because they haven't been exposed previously. Older children, having possibly encountered similar viral strains through previous exposures, might develop cross-reactive immune responses that do not fully protect them but still make them less susceptible to severe forms of the disease (10). The age range of 6 to 19 years often coincides with periods when multiple serotypes of the dengue virus are circulating. Research indicates that secondary infections with different serotypes can significantly increase the risk of severe disease (11,12). Adolescents infected with a serotype different from their previous infection are more likely to experience more severe forms of the illness.

This study showed a significant difference between hematocrit value and dengue severity. Hematocrit, which reflects the proportion of blood volume that is occupied by red blood cells, serves as an important indicator of hemoconcentration—a condition often associated with severe dengue. Higher hematocrit levels, indicating hemoconcentration, which is a common feature in severe cases of

dengue due to plasma leakage (13). This condition is critical because it can lead to complications such as shock and organ failure (14).

Hemoconcentration also showed a significant difference in dengue severity. Several study showed hemoconcentration has association to severity dengue (15–17). Hemoconcentration is one sign of plasma leakage that can lead mild dengue to severe dengue. Hemoconcentration is indicated by elevated hematocrit levels, which reflect an increase in the concentration of red blood cells due to a decrease in plasma volume. Hemoconcentration significantly correlates with increased severity of dengue infection, affecting clinical outcomes such as duration of hospital stay, need for transfusions, and overall mortality risk (14).

Multivariate analysis showed that an increase in hematocrit >15% has risk 6 times to become severe dengue. These results are consistent with a study in Jakarta that an increase in hematocrit >15,1% is one of the signs of plasma leakage that is used as a severe dengue predictor (18). Plasma leakage into the serosal cavity is one of the important stages in severe dengue pathogenesis that will cause hypovolemia, hypotension, edema, shock, and death shock in dengue patients (16). Another study in Jakarta stated that hemoconcentration is at risk 2,5 and 6 times of causing mild dengue to develop into severe dengue (15). Another study in Honduras mentioned that a 15% increase in hematocrit is significant for detecting severe dengue (17).

Increased of hematocrit value is a manifestation of hemoconcentration resulting from plasma leakage to the extravascular space accompanied by serous fluid effusion, via a damaged capillary. As a result of this leak the plasma volume becomes reduced which can lead to hypovolemic shock and circulatory failure. Hemoconcentration serves as a valuable indicator of disease severity and potential complications, thus aiding clinicians in making informed decisions regarding treatment strategies.

5. Conclusion

Based on this study, hemoconcentration can be used as a predictor of dengue hemorrhagic fever severity of infection in pediatric patients in Sleman and Bantul Regional Public Hospital. As a predictor of the severity of dengue hemorrhagic fever infection, hemoconcentration can be used as an early warning for adequate management, preventing shock and further bleeding in pediatric patients.

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