Global Medical and Health Communication

Online submission: http://ejournal.unisba.ac.id/index.php/gmhc
DOI: https://doi.org/10.29313/gmhc.v6i3.3034

GMHC. 2018;6(3):176–81
pISSN 2301-9123 | eISSN 2460-5441

RESEARCH ARTICLE

Clinical and Hematological Parameters as the Predictors of Shock in Dengue Infection

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Abstract

Dengue infection is one of the main health issues in the world and Asia has the highest incidence of dengue infection with most children aged 5–15 years affected. As World Health Organization guidelines recommend, the identification of warning signs at defervescence can detect patients who are at risk of progression to shock. This study aimed to determine the clinical and hematological parameters as the predictors of shock in dengue infection. This retrospective study collected medical records of pediatric patients suffering from dengue infection admitted to dr. Soediran Mangun Sumarso Regional Hospital in Wonogiri, Central Java in January–November 2016. Data was collected in December 2016. The studied predictor factors consisted of clinical and hematological parameters that represented the warning signs of dengue infection. Statistical analysis was performed using the logistic regression test. Of the 110 eligible subjects, 33 (30%) of them suffered from dengue shock syndrome. The multivariate analysis showed that gastrointestinal bleeding (OR=32.62), pleural effusion (OR=31.45), hematocrit >45% (OR=8.67), and thrombocytopenia ≤50,000/µL (OR=13) increased the risk of dengue shock syndrome. Clinical parameters as gastrointestinal bleeding and pleural effusion as well as laboratory parameters of hematocrit and thrombocytopenia became the predictors of shock in dengue infection.

Key words: Dengue infection, predictor factors, shock, warning signs

Parameter Klinis dan Hematologis sebagai Prediktor Kejadian Syok pada Infeksi Dengue

Abstrak

Infeksi dengue merupakan salah satu masalah kesehatan utama di dunia. Asia merupakan kawasan dengan insidensi infeksi dengue tertinggi dengan penderita terbanyak anak berusia 5–15 tahun. *World Health Organization* menyatakan bahwa tanda bahaya dengue pada fase kritis dapat mendeteksi kejadian syok pada pasien. Tujuan penelitian ini adalah menentukan parameter klinis dan hematologis yang menjadi prediktor syok pada infeksi dengue. Penelitian ini merupakan penelitian retrospektif dengan mengumpulkan data rekam medis pasien anak yang menderita infeksi dengue dan dirawat di RSUD dr. Soediran Mangun Sumarso Wonogiri Jawa Tengah pada Januari–November 2016. Pengambilan data dilakukan pada bulan Desember 2016. Faktor prediktor yang diteliti adalah parameter klinis dan hematologis yang merupakan tanda bahaya infeksi dengue. Analisis statistik dilakukan menggunakan uji regresi logistik. Dari 110 subjek penelitian yang memenuhi kriteria, 33 (30%) di antaranya menderita sindrom syok dengue. Analisis multivariat menunjukkan perdarahan saluran cerna (OR=32,62), efusi pleura (OR=31,45), hematokrit >45% (OR=8,67), dan jumlah trombosit ≤50.000/µL (OR=13) meningkatkan risiko sindrom syok dengue. Parameter klinis berupa perdarahan saluran cerna dan efusi pleura serta parameter laboratoris berupa hematokrit dan jumlah trombositopenia merupakan prediktor kejadian syok pada infeksi dengue.

Kata kunci: Faktor prediktor, infeksi dengue, syok, tanda bahaya

Received: 21 September 2017; Revised: 8 December 2018; Accepted: 13 December 2018; Published: 31 December 2018

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Introduction

Dengue infection is a serious health issue in the world. Approximately 2.5–3.6 billion of the world's population living in more than 125 endemic countries are at risk of suffering from this disease.[1] Each year, there are estimated 390 million cases of dengue infection and 96 million cases of clinical manifestations while the rest are asymptomatic cases.[2] Asia is the region with the highest incidence of dengue infection in the world with 5–15 years old children as the most sufferers.[3] In Indonesia alone, the number of dengue infection cases is increasing every year. In 2015, a total of 129,650 cases of dengue hemorrhagic fever (DHF) were reported with 1,071 deaths. The morbidity rate reached 50.75 per 100,000 people with a case fatality rate (CFR) of 0.83%.[4] In Central Java province, DHF remains a serious issue. In 2014, the CFR was 1.7%, which was higher than that in 2013 (1.21%) and even higher than the national target. The CFR of DHF of more than 1% occurred in 23 districts/cities in the province with the highest mortality rate of 9.3% in Wonogiri district.[5]

The clinical manifestations of dengue infection vary greatly from mild dengue fever (DF) to severe infection characterized by severe plasma leakage along with bleeding manifestations named dengue shock syndrome (DSS). To assist clinicians in diagnosing and determining the classification of dengue infection, the World Health Organization (WHO) recommends several criteria for clinical and laboratory diagnosis of dengue.[6] However, predictions of the course of dengue infection or shock in patients remain difficult to make due to the widely varied clinical manifestations among patients, complex pathogenesis, as well as differences in viral serotypes in different regions.[7] The 2009 and 2011 WHO guidelines state that in pediatric patients identification of dengue warning signs based on either clinical symptoms or laboratory findings in the defervescence phase/critical phase of infection has strong discrimination to detect patients who are at risk of severe dengue/shock or to determine whether patients need hospitalization.[6,8]

Studies to prove clinical and laboratory criteria as the risk factors or prognostic factors of the severity of dengue infection in children have been widely performed in Indonesia with varied methods and results.[7,9–13] In general, assessment of the predictors in those studies was conducted without considering the course of the disease/phase of dengue infection. In addition, some of the assessed parameters were not those obtained from routine examination results. Therefore, this study aimed to identify clinical and hematological parameters in the form of dengue warning signs as predictor factors of shock in dengue infection in children carried out in the critical phase of the disease.

Methods

This research was a retrospective study collecting medical record data of DHF patients treated in the pediatric wards of dr. Soediran Mangun Sumarso Regional Hospital in Wonogiri, Central Java from January 2016 to November 2016. Data was collected in December 2016. The inclusion criteria consisted of all patients aged 0–18 years who were diagnosed with dengue infection following the WHO 2011 diagnosis criteria (Table 1).[6] The research subjects were selected through consecutive sampling, and those diagnosed with DF, DHF grade I, and DHF grade II were included in the group of dengue infection in non-shock cases (dengue-NS). Meanwhile, the subjects diagnosed with DHF grade III and IV were categorized in the group of dengue with shock cases (DSS). Subjects were excluded if the medical record was incomplete and the patients had a comorbid infectious disease.

Data was collected from the medical records of dengue patients who were first admitted to hospital during the critical phase of the disease, which was day 3, day 4, or day 5 of fever. Days of illness/fever were calculated from the first day of fever complaint by the patients. The measured predictor factors of shock were the warning signs listed in the WHO 2009 criteria, including clinical parameters in the form of abdominal pain, persistent vomiting, >2 cm hepatomegaly, mucosal bleeding, gastrointestinal bleeding, and plasma leakage signs, as well as hematological parameters consisting of hematocrit level and platelet counts.

Chi-square test was used for the bivariate analysis among predictor variables with prognosis, in which variables with $p<0.25$ would be included in the multivariate analysis. To determine the predictor factors for DSS, the multivariate logistic regression analysis was employed.

This study has received the permit by the Medical and Health Research Ethics Committee, Faculty of Medicine, Universitas Islam Indonesia

Table 1 Classification of Dengue Infection and DHF Grade of Severity

Grades	Signs and Symptoms	Laboratory
DF	Fever accompanied by minimum 2 of the following symptoms: - headache, - retro-orbital pain, - myalgia, - arthralgia, - maculopapular rash, - hemorrhagic manifestations, - no signs of plasma leakage.	- Leucopenia (leukocyte count is ≤5,000 cells/μL). - Thrombocytopenia (platelet count is <150,000 cells/μL). - Hemoconcentration (5–10%). - No evidence of plasma loss.
DHF I	Fever and hemorrhagic manifestations (positive tourniquet test) and signs of plasma leakage.	Thrombocytopenia (<100,000 cells/μL); hemoconcentration (≥20%).
DHF II	Spontaneous bleeding in addition to the manifestations of grade I.	Thrombocytopenia (<100,000 cells/μL); hemoconcentration (≥20%).
DHF III	Manifestations of grade I or II along with circulatory failure (weak pulse, ≤20 mmHg pulse pressure, hypotension, restlessness, decreased diuresis).	Thrombocytopenia (<100,000 cells/μL); hemoconcentration (≥20%).
DHF IV	Profound shock with undetectable blood pressure and pulse.	Thrombocytopenia (<100,000 cells/μL); hemoconcentration (≥20%).

Yogyakarta by ethics approval letter number: 73/Ka.Kom.Et/70/KE/XI/2016.

Results

During the research period, 110 dengue infection patients admitted to the pediatric wards of dr. Soediran Mangun Sumarso Regional Hospital in Wonogiri, Central Java fulfilled the inclusion criteria. Characteristics of the subjects are presented in Table 2. Most of them were male (52%) with a proportion of 1.07:1 compared to female. The age of 49% of the research subjects ranged 10–14 years. The percentage of the subjects admitted to the hospital on 3rd and 5th day of fever was each 34%, while 33% of them were admitted on day 4.

Based on the final diagnosis, the subjects were divided into two groups, namely dengue patients with shock cases (DSS) of 33 people (30%) and dengue patients in non-shock cases (dengue-NS) totaling 77 people (70%). Table 3 shows that clinical manifestations of acral coldness, gastrointestinal bleeding, pleural effusion, and petechiae were more common in DSS patients than in non-shock dengue patients, with percentages

Table 2 Characteristics of the Subjects

Characteristics	Number (n=110)	Percentage (%)
Sex		
Male	57	52
Female	53	48
Age (years)		
0–4	12	11
5–9	29	26
10–14	49	45
≥15	20	18
Day of fever when first admitted to hospital		
3rd	37	34
4th	36	33
5th	37	34

Table 3 Clinical Parameters

Clinical Manifestations	Dengue-NS 77 (70%)	DSS 33 (30%)	p Value
Abdominal pain	38 (68%)	18 (32%)	0.617
Persistent vomiting	50 (68%)	23 (38%)	0.628
Hepatomegaly >2 cm	42 (59%)	29 (41%)	0.001*
Accumulation of fluid			
Ascites	46 (59%)	32 (41%)	0.000*
Pleural effusion	22 (43%)	29 (57%)	0.000*
Hemorrhagic manifestation			
Petechiae	21 (45%)	26 (55%)	0.000*
Gum bleeding/epistaxis	17 (63%)	10 (37%)	0.358
Gastrointestinal bleeding	2 (22%)	7 (78%)	0.003*

*p<0.05, statistically significant

Table 4 Hematological Parameters

Hematological Parameters	Dengue-NS 77 (70%)	DSS 33 (30%)	p Value
Hematocrit >45%	16 (42%)	22 (58%)	0.000*
Thrombocytopenia ≤50,000/µL	42 (58%)	31 (42%)	0.000*

*p<0.05, statistically significant

of 100%, 78%, 57%, and 55%, respectively. The most common clinical manifestations in non-shock dengue patients were abdominal pain (68%), persistent vomiting (68%), gum bleeding/epistaxis (63%), hepatomegaly (59%), and ascites (59%). Hematological abnormality in the form of hematocrit level of >45% was more commonly found in DSS patients than in non-shock dengue patients, reaching 58% as shown in Table 4.

The bivariate analysis using a chi-square test showed that clinical and hematological parameters based on warning signs that distinguish DSS from non-shock dengue were hepatomegaly >2 cm, ascites, pleural effusion, gastrointestinal bleeding, hematocrit >45%, and thrombocytopenia ≤50,000/µL.

The results of logistic regression analysis indicated that the clinical symptom parameters in the form of gastrointestinal bleeding (OR=32.62) and pleural effusion (OR=31.45) in a multivariate manner had a significant effect on shock cases with 5% significance level. In addition, the laboratory parameters as the predictors of shock in this study included thrombocytopenia ≤50,000/µL

Table 5 Logistic Regression Analysis for DSS Predictor Factors

Characteristics	Coef.	p Value	OR	95% CI	
				Min.	Max.
Clinical parameter					
Gastrointestinal bleeding	3.48	0.002*	32.62	3.50	303.95
Pleural effusion	3.45	0.000*	31.45	6.91	143.11
Constant	−3.35	0.000	0.04		
Hematological parameter					
Hematocrits >45%	2.16	0.000*	8.67	2.97	25.33
Thrombocytopenia ≤50,000/µL	2.57	0.002*	13.00	2.49	67.91
Constant	−0.48	0.219	0.62		

*p<0.05, statistically significant

(OR=13), and hematocrit >45% (OR=8.7).

Discussion

The cases of DSS were found in 30% of 110 patients with dengue infection who met the inclusion criteria. This is not much different from the DSS cases in several other studies ranging 30–40%.[7,12] In this study identified several DSS predictors indicating warning signs of dengue infection listed in WHO guidelines. Warning signs are a collection of signs and symptoms that precede shock manifestations, enabling them to be used as a prognosis for DSS cases. Such signs appear at the end of the acute phase because of increased capillary permeability.[8] Endothelial dysfunction leads to capillary permeability due to the release of inflammatory mediators triggered by proinflammatory cytokines. Such cytokines are produced by the cells infected with dengue virus.[14]

Accumulation of fluid in tissues, including ascites and pleural effusion, is a manifestation of plasma leakage due to increased capillary permeability. This clinical sign appears at the beginning of the critical phase.[8] In this study, pleural effusion had a highly significant correlation with DSS cases in children and was an important predictor factor (OR=31.45). These results are consistent with several previous studies.[12,13]

The incident of gastrointestinal bleeding in this study was more common in subjects with DSS than in non-shock cases, making it a strong predictor factor with OR=32.62. This finding is in line with other studies.[7,12,13,15] Gastrointestinal bleeding is closely related to thrombocytopenia in severe dengue infection.[16,17] The degree of severity of thrombocytopenia is directly proportional to the severity of hemorrhagic manifestations. In dengue patients, platelet counts of <50,000/μL have a significant association with severe bleeding.[18]

Hepatomegaly clinical manifestation is a fairly common prognostic factor of DSS.[7,11–13,15] Abdominal pain is an early indicator of increased capillary permeability and is a prognostic factor for predicting the severity of dengue infection.[11,16] It can be caused by gastrointestinal bleeding, hepatomegaly, or tissue hypoxia due to insufficient visceral blood supply during the condition of pre-dengue and dengue shock.[10] In this study, abdominal pain and hepatomegaly were more common in non-shock dengue patients than in those experiencing DSS, indicating that they were not the prognostic factors of DSS. This is likely due to the limitations in confirming complaints and examination results to the research subjects because the data was taken only from the patients' medical records.

In this study, the laboratory parameter, the hematocrit >45%, is a predictor factor for DSS cases (OR=8.67) similar to the finding of previous studies.[7,11–13,15] Increased hematocrit level above normal is one of the initial signs of plasma leakage. High hematocrit level is associated with the severity of plasma leakage. Such plasma leakage will reach its peak during a shock event.[8]

The platelet count of ≤50,000/μL in this study also increased the risk of DSS (OR: 13.00). Thrombocytopenia is a prognostic factor of shock in dengue as suggested by previous studies.[7,9,11–13,15] Thrombocytopenia in DHF patients results from a decrease in platelet production by the bone marrow, which is temporarily suppressed, as well as an increase in platelet destruction in the peripheral circulation. Bone marrow suppression is a direct result of damage to hematopoietic cells due to dengue virus attacks, or as a result of dengue virus infection in stromal cells that triggers the production of proinflammatory cytokines. Increased peripheral platelet destruction is caused by several mechanisms such as imbalance between coagulation factor and fibrinolysis factors, autoimmune processes that attack platelets, direct interaction between dengue virus and platelets, as well as interaction between platelets and endothelial cells or monocytes/neutrophils that cause activation and destruction of platelets at once.[19]

Gastrointestinal bleeding, pleural effusion, hematocrit level of >45%, and thrombocytopenia ≤50,000/μL are the clinical and laboratory parameters that become the predictors of shock in dengue infection. These predictor factors are expected to be the warning sign that can improve accuracy, alertness, and monitoring of patients with dengue infection.

Conclusion

Clinical parameters as gastrointestinal bleeding and pleural effusion as well as laboratory parameters of hematocrit and thrombocytopenia became the predictors of shock in dengue infection.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgement

Thank you to the Head of the Undergraduate Medical Education Program, Faculty of Medicine, Universitas Islam Indonesia, Yogyakarta that has provided the funding for this research through the Hibah Kinerja II program. We also thank you to the Director of dr. Soediran Mangun Sumarso Regional Hospital in Wonogiri, Central Java and all the staff who have given permission to and assisted the researchers during the study.

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