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The worsening factors of dengue hemorrhagic fever (DHF) based on cohort study with nested case-control in a tertiary hospital

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Abstract. The clinical pathway of DHF has a broad pathophysiological and pathogenesis spectrum. Clinical and laboratory characteristics are some of the parameters to determine the factors that contribute to the worsening of the disease. The objective of this study is to determine the clinical and laboratory characteristics which contribute to the worsening of DHF. The study had been conducted from January 2012-December 2014 at the general ward of the Internal Medicine Department, Indonesia Army Central Hospital Gatot Soebroto. There were 101 male patients (64.7%) and 55 female patients (35.3 %) ages ranging from 14 - 62 years old. The diagnosis was divided into: 124 patients DHF grade I, 6 DHF grade II, 20 DHF grade III and 6 with dengue shock syndrome (DSS) patients. Clinically and statistically, there were 4 variables apparently found with the severity of DHF, as follows: decreased appetite with $p = 0.007$ (OR 4.87), hepatomegaly with $p = 0.009$ (OR 27.00), systolic blood pressure with $p = 0.037$ (OR 0.95), and initial thrombocyte with $p = 0.000$ (OR 0.97). This cohort and nested case-control study found that worsening of DHF is related with decreased appetite, hepatomegaly, systolic blood pressure and initial thrombocyte count.

1. Introduction

Dengue is an acute fever caused by the dengue virus (DENV) which is distinguished into four serotypes (DENV-1-4). This virus belongs to the Flaviviridae family, which is from flavivirus genus. The symptoms of the disease are high fever, headache, abdominal pains, rashes, myalgia, and arthralgia. dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS) are the severe forms of the disease. The pathogenesis hallmark of the disease are thrombocytopenia, vascular leakage and hypotension.[1]



Currently, the prevalence of the dengue virus infection is quite high in the world. The WHO data across 70 countries in the world revealed that there were 925,896 cases of dengue fever and dengue hemorrhagic fever in 2000-2007.[2,3]

Dengue has a wide and varied spectrum of clinical manifestations, from asymptomatic to symptomatic condition. The WHO guideline used for the disease is the chronological process, beginning from fever up to the critical and recovery phase. The above processes are important for the clinical and immunopathogenesis approach in order to monitor the treatment optimally.[4] The clinical manifestation of dengue shows the specific process which determines the presence of plasma leakage (worsening) thereafter. Apart from it, the clinical sign also revealed the critical point of the worsening of the dengue hemorrhagic fever. The previous study also revealed that the tourniquet test might show vasculopathy (petechiae). Meanwhile, a thrombocyte count of less than 50000, hepatomegaly, and pleural effusion (ascites) show a plasma leakage.[5]

The theory of DHF predictive factors by Guzman and Kouri introduces the integral hypothesis theory which states that the risk factors of the worsening DHF and DSS are composed of individual, viral, and epidemiological factors. Individual factors consist of age, sex, race, nutrition, secondary infection and host response. Viral factors consist of the strain and serotypes of the virus. The epidemiological factors consist of the case number, identity of virus, virulence and hyperendemic.[6] Juffrie, *et al* held a case-control study to reveal the predictors of shock using odds ratio (OR). The factors that were statistically related to shock were ascites (OR 5.1), cold extremity (OR 9.8), ecchymosis (OR 4.6), pleural effusion (OR 10.7), lowest thrombocytopenia (OR 5.9), and plasma protein (OR 7.3). The minimal odds ratio of this study, which reflects how strong the study is in detecting the relationship power, was 3 so hepatomegaly (OR 2.2) and highest hematocrit (OR 1.5) are statistically but not clinically significant. This study did not reveal a shock prediction model.[7] Hadinegoro, by using a cross-sectional study found that the variable of the lowest thrombocyte was statistically significant as a predictor of the worsening condition in dengue hemorrhagic fever patients in mild stage, while the variable of hemoconcentration, endotoxemia, and IL-6 were considered clinically significant. This study introduced a predictor model but did not make a scoring system.[8] The case-control study by Gayatri showed that the highest hematocrit (OR 1.08), the lowest thrombocytopenia (OR 1.00), the fever (OR 1.31), and the age (OR 0.85) were all significant as shock predictors. These variables were measured in numeric scale. This study also introduced a predictor model but did not make a scoring system.[9] A study by Dewi confirmed that the hepatomegaly (OR 2.4) and the lowest thrombocyte (OR 4.4) were shock predictors. The OR of hematocrit was 1.7 which made it clinically, not statistically, significant. The study introduced another predictor model but not the scoring system.[10] Another case-control study by Triono found that the hepatomegaly (OR 11.08) and the initial hematocrit (OR 8.9) were statistically significant as shock predictors. However, the initial thrombocytopenia (OR 2.2) and leukocyte (OR 2.3) were clinically but not statistically significant.[11]

The objective of this study is to determine the clinical and laboratory characteristics which contribute to the worsening of the DHF through the cohort and nested-case control study that had been conducted from January 2012 – December 2014 at the general ward of the Internal Medicine Department, Indonesia Army Central Hospital Gatot Soebroto.

2. Materials and Methods

2.1. Sampling Size and Sampling Method

The Ethical Committee of the Faculty of Medicine, Universitas Gadjah Mada, Ref. No : KE/FK/719/EC approved the study on July 29th, 2013. The subject of this study was 156 dengue-infected patients of which 101 (64.7%) were males and 55 (35.5 %) females, age ranging from 14 to 62 years old. The grouping of all patients was done based on the clinical criteria of WHO 1997 and WHO 2009. The worsening criteria of the DHF were marked by the presence of plasma leakage consisting of increasing hematocrit and decreasing blood pressure during the critical phase. This study

used the consecutive sampling for the cohort design and the stratified random sampling for the nested case-control design (*Win Papi version 11.28 software*).

2.2. Investigation

All patients were questioned for symptoms and clinical signs of dengue fever (for example temperature, blood pressure, heartbeat, and body weight). The patients also had to undergo a laboratory evaluation and a complete blood count such as hematocrit, thrombocyte, leukocyte, liver, kidney function test, and dengue serology (IgG and IgM) as indicated in the criteria of inclusion. The patients had to undergo a complete blood count tests on the fourth day of hospitalization and an organ function evaluation on the seventh day. All patients were then observed in cohort with nested case-control to discover whether the disease worsened or not.

2.3. Statistical Analysis

The researchers performed a multivariate analysis of the factors related to the worsening of dengue fever using the Hosmer and Lemeshow test. The differences in the value of the hemoglobin (Hb), hematocrit (Ht), and thrombocyte between patients with worsening and non-worsening dengue was evaluated with an-paired-test and corrected with Bonferroni and Mann-Whitney test.

3. Results

There were 156 patients who fulfilled the inclusion criteria. Out of 156, 124 were diagnosed with dengue hemorrhagic fever (DHF) grade I, 6 with DHF grade II, 20 with DHF grade III, and 6 with dengue shock syndrome (DSS). In this study, 26 patients initially diagnosed with DHF grade I had their disease worsened into DHF grade III/ DSS.

Table 1. Multivariate analysis of factors related to the worsening of DHF.

Predictors	p-value	OR	Confident Interval	
			Min	Max
Decrease of appetite	0.007	4.87	1.54	15.43
Hepatomegaly (+)	0.009	27.00	2.26	322.46
Systole	0.037	0.037	0.90	1.00
Initial thrombocyte (x10 ³)	0.000	0.97	0.95	0.99

Table 2. Comparison of Hb, Ht, and thrombocyte between patients with worsening DHF and non worsening DHF.

		Worsening DHF (n=26)	Non-worsening DHF (n=130)	p value
Hb	Initial	15.45±2.69	14.67±1.56	0.047 ^a
	4-5 th day	14.52±2.02	14.12±1.52	0.261 ^a
	7 th day	13.25±1.91	14.02±1.57	0.030 ^a
Leukocyte	Initial	3300 (1300-7300)	3350 (1400-9960)	0.341
	4-5 th day	4400 (1500-21440)	4250 (1200-11400)	0.998
	7 th day	6250 (1900-13000)	5520 (2000-11700)	0.140
Ht	Initial	44.62±6.97	43.15±4.62	0.179 ^a
	4-5 th day	40.96±6.38	41.85±4.40	0.391 ^a
	7 th day	38.69±5.21	41.23±4.72	0.015 ^a
Thrombocyte	Initial	59500 (7000-121,000)	93000 (13000-204,000)	<0.001 ^b
	4-5 th day	28500 (5000-105,000)	57500 (11000-165,000)	<0.001 ^b
	7 th day	90000 (20000-193,000)	106,500 (13000-259,000)	0.165 ^b

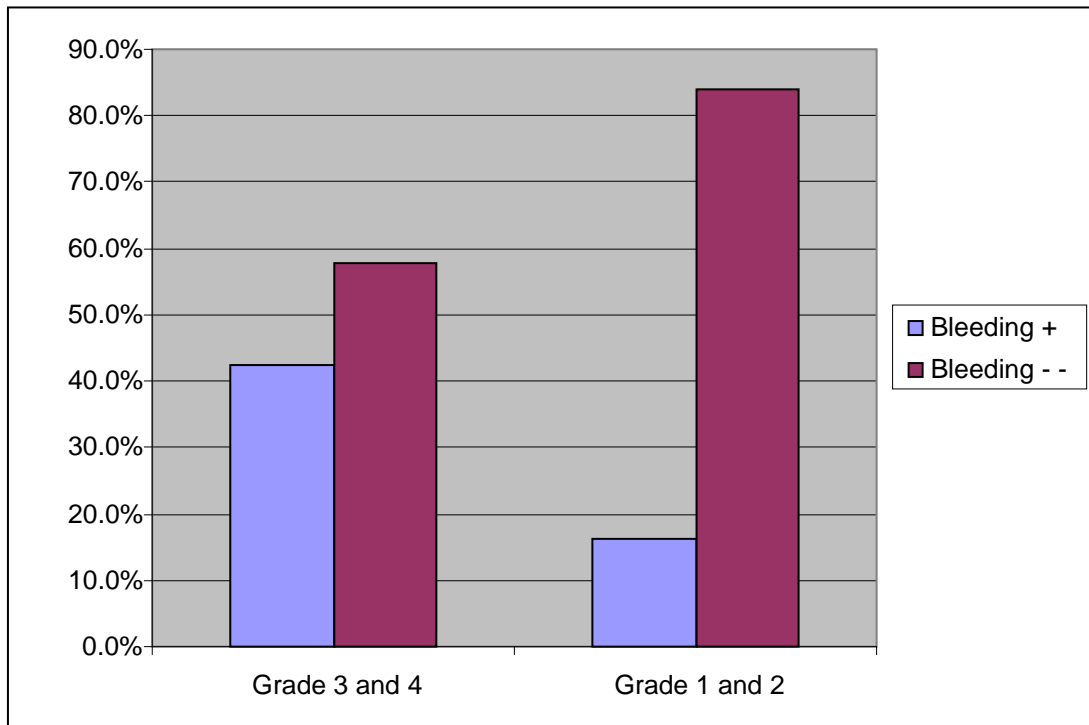


Figure 1. Characteristics of petechiae in patients with DHF grade I and grade III (p 0.003).

4. Discussion

Dengue hemorrhagic fever (DHF) with its annual cycle of an unusually high number of cases remains a scientific challenge to be studied on. Both epidemiological aspects and patient management aspects are still widely opened for further research. Epidemiological aspects and surveillance are related to promotive and preventive measures while patient management aspect is related to diagnosis and optimal treatment of the disease. Both of these aspects are connected with the pathogenesis of the disease which manifests as various spectrums of clinical conditions. Therefore, a parameter is needed in order to determine which predictor factors contribute to the worsening of the disease.[3]

One hundred and fifty-six patients with dengue fever were included in this study, 101 of which were male (64.7%), and the other 55 were female (35.3%). The age range was between 14 to 62 year old with a mean age of 28.73 ± 10.09 year old. Out of 156 patients, 124 patients were classified as DHF Grade I, 6 patients as DHF Grade II, 20 patients as DHF grade III, and 6 patients as DSS. The most prominent signs and symptoms found on Grade I patients were headache (82.0%), nausea and vomiting (81.6%), decreased appetite (70.4%), joint pain (83.5%), and retro-orbital pain (81.4%). Petechiae was found in 69.2% patients with DHF Grade I and 30.8% patients with DHF Grade III. The relationship between some clinical variables and demographical characteristics are as followed: duration of fever with OR of 1.29, headache with OR of 6.72, decreased appetite with OR of 6.72, retro-orbital pain with OR of 1.28, Rumpel leed with OR of 1.44, hepatomegaly with OR of 23.45 and bleeding signs with OR of 3.81. Based on physical examination and laboratory evaluation, systolic blood pressure has a p-value of 0.051; initial thrombocyte has a p-value of < 0.0001 . After performing multivariate analysis for factors related to worsening of DHF using Hosmer and Lemeshow Test step 9, four variables were found to be clinically and statistically related with the worsening of the disease. Those variables were decreasing appetite with p 0.007 (OR 4.87), hepatomegaly with p 0.009 (OR 27.00), systolic blood pressure with p 0.037 (OR 0.95) and initial thrombocyte count with p 0.000 (OR 0.97).

5. Conclusion

This cohort and the nested case-control study found that worsening of DHF is related with decreased appetite (p 0.007), hepatomegaly (p 0.009), systolic blood pressure (p 0.037) and initial thrombocyte count (p 0.000).

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