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*Research Article*

# Hematological Test : Predicting Incidence Dengue Shock Syndrome

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## Abstract

Dengue hemorrhagic fever (DHF) is an infectious disease caused by the Dengue virus. DHF cases in Mataram City from 2016 to 2020 tend to increase where most of the DHF patients are treated at the Mataram City Hospital. Death due to DHF infection mostly occurred in patients with Dengue Shock Syndrome (DSS) and mortality from DSS was reported to be 50 times higher than in DHF patients without DSS. Prompt diagnosis and appropriate treatment are important determinants for the prevention and control of dengue cases, so knowing the predictors of risk factors can prevent/reduce deaths from dengue virus. This study used a case-control design. Cases were DHF patients diagnosed with DSS by the treating doctor, while the controls were DHF patients diagnosed not DSS by the treating doctor. The research data was obtained from the results of laboratory tests stored in the medical records of patients treated at the Mataram City Hospital from January 2016 to December 2020. The design of the analysis was aimed at obtaining the odds ratio (OR) value followed by multivariate analysis to determine the risk factors that could detect DSS earlier. The variables that were statistically significant in the prediction of the final model were the increase in hematocrit value > baseline with OR= 17.1 (95% CI: 4.033-72.600), a decrease in platelet value < 100.000/µL with OR = 6 (95% CI). : 2,306-15,699), and decreased leukocyte value < baseline with OR= 5.1 (95% CI: 2,209-11,838). While the most dominant variable is the increase in hematocrit value > baseline with OR = 17.1 (95% CI: 4.033-72.600) and p value = 0.000.

**Keywords:** Hematology, hematocrit, platelets, leukocytes, DHF, DSS

## 1. Introduction

Dengue Hemorrhagic Fever (DHF) is a disease caused by dengue virus infection which is transmitted through the bite of the female mosquito vector Aedes aegypti, Aedes albopictus, and Aedes scutellaris (Ministry of Health, 2017) with the characteristics of sudden high fever accompanied by various clinical manifestations. from asymptomatic to plasma leakage resulting in Shock Syndrome (DSS). Dengue virus infection clinically manifests itself as asymptomatic or can cause indistinguishable fever (viral syndrome), dengue fever, or dengue hemorrhagic fever (DHF) including Dengue shock syndrome (DSS) (Arsin, 2013). Dengue classification according to WHO SEARO 2011 which is an extension of the 1997 WHO classification is believed to be more suitable for the situation in Indonesia. The classification is divided into Dengue Fever (DD), Dengue Hemorrhagic Fever (DHF) grades I, II, III, and IV plus the Expanded Dengue syndrome (EDS) classification. Clinical manifestations also depend on the strain of the virus and host factors such as age and antibodies (WHO, 2011).

In the modeling it is estimated that around 390 million dengue virus infections annually (95% CI = 284-528 million), of which 96 million (67-136 million) manifest clinically (Samir, 203). Another study estimates that the prevalence of dengue is around

3.9 billion people at risk of contracting dengue virus with 129 countries at risk of dengue virus infection with 70% in Asia (Brady, 2012). WHO reported an 8-fold increase in the number of dengue cases over the last two decades, from 505,430 cases in 2000 to more than 2.4 million cases in 2010, and 4.2 million cases in 2019 reported deaths between 2000 and 2015 increased from 960 cases to 4032 cases (WHO, 2020).

The division of diagnostic criteria for dengue virus infection is divided into clinical criteria and laboratory criteria. The clinical criteria are headache, sudden onset of fever for 2-7 days, bleeding manifestations, thrombocytopenia (platelets 100,000/mm3), plasma leakage marked by an increase in hematocrit 20% from the baseline value, and the presence of hepatomegaly until shock occurs. Laboratory criteria are said to be probable if the clinical diagnosis is confirmed by the results of anti-Dengue serologic test, and said to be confirmed if the clinical diagnosis is confirmed by the Haemagglutination-Inhibition (HI test) examination, positive results are obtained on tissue autopsy examination or seroconversion of IgG and IgM examinations on paired serological examinations, and/or or on examination using Polymerase Chain Reaction (PCR) with positive results (WHO, 2011).

DHF if not handled properly will result in death in a short time, therefore it is necessary to watch out for the cause of death in DHF patients. Death due to Dengue not only comes from the accuracy of the diagnosis before being referred, but the handling and treatment given to the patient also has an important role. The probability of death from DHF in patients who do not receive adequate fluid resuscitation is 1.5 times greater (Ruri, 2018). Excess fluid is an important complication in treating shock, and heavy bleeding in the digestive tract after a prolonged and untreated shock is another cause of DHF death. (WHO, 2011) The high incidence and mortality of DHF patients cannot be separated from the risk factors for DSS, such as: age, gender, delayed treatment and referral status, nutritional status, immunological status, prolonged shock, and viral serotype (Gerald, 2021).

Based on the results of a preliminary survey conducted in 2021 that of the 17 hospitals in Mataram City, 85% of DHF patients were treated at the Mataram City Hospital and most of the DSS cases were treated at the hospital. Based on data from medical records and the electronic data center of the Mataram City Hospital in 2017, there were 428 cases of DHF, in 2018 there were 131 cases of DHF, in 2019 there were 956 cases, and in 2020 there were 1,014, with a total of DSS cases in During that period, there were 78 cases of DSS. (NTB Provincial Health Office, 2020) Based on the data above, it is necessary to conduct research on the risk factors for the occurrence of Dengue Shock Syndrome in Dengue Hemorrhagic Fever patients at the Mataram City General Hospital.

## 2. Materials and Methods

This study is an analytical observational study with a case control study design to determine the relationship between exposure and disease. This research was conducted from April 2021 to June 2021 at the Mataram City Hospital, West Nusa Tenggara. The data

used in this study is secondary data originating from the medical records of patients treated at the Mataram City Hospital, West Nusa Tenggara for the period January 2016 to December 2020. The sampling technique in this study was carried out by Probability Sampling with a systematic random sampling technique, The minimum sample size determined in this study was 56 respondents for the case group, while for the control group as many as 112 respondents, using a ratio between the case group and control group of 1:2 so that the total sample was 168 respondents.

## 3. Results and Discussion

### 3.1 Results

Univariate analysis was carried out to see the description of the frequency distribution and the proportion of characteristics of the risk factor variables found in the case group and control group studied in this study. Risk factors consist of increased hematocrit value, decreased platelet value, decreased leukocyte value, age, gender, nutritional status, length of illness, and the referral process. The results of the univariate analysis in this study can be seen as follows:

**Table 1.** Distribution of the Number of Respondents Based on the Diagnosis of Risk Factors for DSS Incidence in Patients with DHF at the Mataram City Hospital in 2016-2020

| No | Case Diagnosis | n | % |
|---|---|---|---|
| 1 | DSS | 56 | 33,3 |
| 2 | Non-DSS | 112 | 66,7 |
| **Total** | | 168 | 100 |

The use of this multivariate analysis aims to see the relationship between risk factors and the incidence of DSS, so that it can be estimated the magnitude of the relationship between the independent variable and the dependent variable after controlling for other variables. Logistic regression analysis is a mathematical model used to analyze the relationship of one or several independent variables with a dependent variable. The multivariate analysis conducted in this study used multivariate logistic regression analysis with predictive models and backward stepwise (likelihood ratio) methods.

From the results of these activities, the final model in this study was obtained based on multivariate logistic regression analysis using the backward stepwise method (likelihood ratio), as shown in the table below:

**Table 2.** Final Modeling Results of Logistics Regression

| No | Variable | B | OR | 95% CI | | p-value* |
|---|---|---|---|---|---|---|
| | | | | *Lower* | *Upper* | |
| 1 | Decrease in Leukocyte Value | 1,632 | 5,1 | 2,209 | 11,838 | 0,000 |
| 2 | Decrease in Platelet Value | 1,794 | 6 | 2,306 | 15,699 | 0,000 |
| 3 | Increase in Hematocrit Value | 2,840 | 17,1 | 4,033 | 72,600 | 0,000 |

*) p-value < 0.05

From table 5.6, it is known that the variables that were statistically significant related to the incidence of DSS in the Mataram City Hospital in 2016-2020 were the variable increasing the hematocrit value with OR = 17.1 (95% CI: 4.033-72.600), decreased platelet value with OR = 6 (95% CI: 2,306-15,699), and decreased leukocyte value with OR= 5.1 (95% CI: 2,209-11,838).

Based on the results of the multivariate analysis model above, it can be concluded that DHF patients who experienced an increase in the hematocrit value > baseline had a 17.1 times chance of experiencing DSS compared to the hematocrit value baseline. Patients with DHF who have decreased platelet values < 100,000/ 100.000L have 6 times the chance of experiencing DSS compared to platelet values 100,000/µL. Meanwhile, for DHF patients who experienced a decrease in the leukocyte value < baseline, the chance of experiencing DSS was 5.1 times compared to the leukocyte value > baseline.

From the results of the final model of multivariate analysis, it can be concluded that the variables that affect the incidence of DSS are an increase in hematocrit, a decrease in platelets, and a decrease in leukocytes. While the most dominant variable is the increase in hematocrit value > baseline with OR = 17.1 (95% CI: 4.033-72.600) and p-value = 0.000.

## 3.2 Discussion

### 3.2.1 Increase in Hematocrit Value

Indications of plasma leakage can be seen from the hematocrit examination. Hematocrit assessment is a sensitive indicator of plasma leakage, so it is necessary to periodically check the hematocrit. In general, the decrease in platelets precedes the increase in the hematocrit. Hemoconcentration with an increase in hematocrit 20% (eg hematocrit from 35% to 42%), reflects increased capillary permeability and plasma permeation. It should be noted that the hematocrit value is affected by fluid replacement or bleeding. To get the calculation of the difference between the highest and lowest hematocrit values, it can only be calculated after getting the hematocrit values during acute and convalescent (7th day) (WHO, 2011).

In this study, it was found that 30.4% of DSS patients experienced hemoconcentration, this was greater than hemoconcentration in DHF patients. Hemoconcentration can occur due to a decrease in blood plasma levels due to vascular leakage. (Johanus, 2019) The reference value used in the hematocrit laboratory test at the Mataram City Hospital varies slightly due to the sensitivity of the test equipment used.

However, the average increase in the hematocrit value in the case and control groups was 20%. To measure the increase in hematocrit, researchers refer to the reference value or baseline laboratory test results.

Based on the results of statistical tests in multivariate analysis, it was also found that the value of p = 0.000 which means that there is a statistically significant relationship. This shows that an increase in hematocrit > baseline has a significant relationship with the occurrence of DSS (OR= 17.1; 95% CI: 4.033-72.600). Patients with DHF who experienced an increase in hematocrit value > baseline had a 17.1 times chance of experiencing DSS compared to the hematocrit value baseline.

The results of the study above are in line with the research conducted by Pujiarti (2016) and Harisnal (2012) explaining that there is a relationship between hematocrit levels and the incidence of DSS (OR = 7.86; 95% CI: 2.748-22.500). Cecillia (2019) also explained the same thing, an increase in hematocrit value had a significant relationship with the incidence of DSS (OR = 4.72). The same thing is also explained in Vijayaraghavan's research (2020), that an increase in the hematocrit value can be a predictor for the occurrence of DSS. Rahmasari (2020) revealed that, an increase in the hematocrit value can be one of the parameters to detect DHF with a DSS tendency. Patients with elevated hematocrit levels should be treated with incentives because they have a greater chance of developing DSS compared to patients who do not have elevated hematocrit levels.

However, the results of this study obtained a wide 95% confidence interval both in the bivariate analysis of increasing the hematocrit value (95% CI: 4.4-57) and in the multivariate analysis (95% CI: 4.033-72.6). The wide confidence interval value can be caused by the small number of samples in the research cell. We know that the confidence interval is related to the magnitude of the association and the accuracy of the estimate. This indicates that there is still a chance effect on the results of the study. (Sheng, 1998) However, statistical analysis was able to predict the relationship of risk factors to the incidence of DSS, so it would not affect the significance of the relationship.

### 3.2.2 Decrease in Platelet Value

A decrease in the platelet count precedes an increase in the hematocrit value. Thrombocytopenia is a condition when the number of platelets (platelets) is low below the normal value. According to WHO, mild thrombocytopenia values range from 100,000 cells/mm3-150,000 cells/mm3, but most occur and about half of all events have values <100,000 cells/mm3, and for severe thrombocytopenia <50,000 cells/mm3, this is rare. (WHO, 2011). A previous study conducted by Edwin (2019) explained that a platelet level 50,000/mm3 was a significant risk factor for DSS (Johanus, 2019). This is in line with the results of research conducted by Peasetya (2017) showing that there are four variables that influence and cause DSS events in DHF patients with a probability or risk level of 94.51%, one of which is a thrombocytopenia value <50,000µL . (Dias, 2017)

The results of the multivariate test showed that there was a significant relationship between a decrease in platelet value < 100,000 /L with the occurrence of DSS (OR= 6; 95% CI: 2,306-15,699). This is in line with a retrospective cohort study conducted in Thailand explaining the characteristics that increase the risk of DSS occurrence, one of which is the platelet value 100,000/µL (OR= 10.60). A study conducted by Lam (2017) on 2,301 children suffering from DHF in Vietnam explained that the daily platelet count showed a better ability to predict the incidence of shock in children. A study with a platelet value < 50,000 /L conducted by Mulyaningrum (2018) explained that a platelet count 50,000/µL increased the risk of DSS (OR= 13).[63] Prameswari (2018) in his research revealed the same thing, a platelet count < 50,000/µL has a 2.32 times greater risk of experiencing DSS, and in the conclusion of his research, the number of platelets values can be used as a prognostic indicator for the occurrence of DSS.

It is known that the results of this study obtained a wide 95% confidence interval both in the bivariate analysis of platelet decline (95% CI: 2.92-16.7) and in the multivariate analysis (95% CI: 2.306-15.699). The wide confidence interval value can be caused by the small number of samples in the research cell. We know that the confidence interval is related to the magnitude of the association and the accuracy of the estimate. This indicates that there is still a chance effect on the results of the study (Shang, 1998). However, statistical analysis can predict the relationship of risk factors to the incidence of DSS, so it will not affect the significance of the relationship.

### 3.2.3 Decreased Leukocyte Value

White blood cells (leukocytes) can vary in their count. In cases of DHF, where the leukocyte count may be normal, but in the early stages there is generally leukopenia with a predominance of neutrophils. Towards the end of the febrile phase and the beginning of shock, there is a decrease in leukocytes (WHO, 2011) Counting the type of leukocyte is a calculation of the type of leukocyte present in the blood based on the percentage proportion of each type of leukocyte from the total number of leukocytes. For a normal leukocyte count of 3,200 mm3 – 10,000 mm3 in adult humans (Diana, 2015). The reference value used in the leukocyte laboratory test at the Mataram City Hospital varies slightly due to the sensitivity of the test equipment used. To measure the decrease in leukocyte values, researchers refer to the reference value or baseline laboratory test results. It is known that 50% in the case group of DSS patients experienced a decrease in leukocytes, this was greater than in the control group.

From the results of statistical tests using multivariate analysis, it is known that there is a significant relationship between a decrease in the value of leukocytes < baseline with the incidence of DSS (OR = 5.1), meaning that DHF patients who experience a decrease in the value of leukocytes < baseline have a 5.1 times risk of developing DSS compared to those with DSS. leukocyte value baseline (95% CI: 2,209-11,838). This is in line with the research conducted by Harisnal (2012) and Podung (2021) explaining that the leukocyte

value < 4000 mm3 is a risk factor for DSS. Safari (2018), explains the same thing, a decrease in leukocyte value is significantly related to the incidence of DSS.

The 95% confidence interval was wide in both the bivariate analysis of leukocyte decline (95% CI: 2.38-10) and in the multivariate analysis (95% CI: 2.209-11.838). The wide confidence interval value can be caused by the small number of samples in the research cell. We know that the confidence interval is related to the magnitude of the association and the accuracy of the estimate. This indicates that there is still a chance effect on the results of the study (Shang, 1998). However, statistical analysis can predict the relationship of risk factors to the incidence of DSS, so it will not affect the significance of the relationship.

## Conclusion

Based on the multivariate test, there was a significant relationship between the decrease in leukocyte values < baseline and the incidence of DSS with p value = 0.000 and OR = 5.1 (95% CI: 2,209-11,838). p = 0.000 and OR = 6 (95% CI: 2.306-15.699), and between an increase in hematocrit value > baseline and DSS incidence with p = 0.000 and OR = 17.1 (95% CI: 4.033-72.600).

## References

Arsin, A.A., *Epidemiologi Demam Berdarah Dengue (DBD) di Indonesia*. 2013, Makasar: Masagena Press.

Brady, O.J.G., P. W. Bhatt, S. Messina, J. P. Brownstein, J. S. Hoen, A. G. Moyes, C. L. Farlow, A. W. Scott, T. W. Hay, S. I., *Refining the global spatial limits of dengue virus transmission by evidence-based consensus.* PLoS Negl Trop Dis, 2012. **6**(8): p. e1760.

Gerald C. D. Podung, S.N.N.T., Max F. J. Mantik, *Faktor Risiko Terjadinya Sindroma Syok Dengue pada Demam Berdarah Dengue.* Jurnal Biomedik (JBM), 2021. **13**: p. 161-166.

Kemenkes, (2017). *Pedoman Pencegahan dan Pengendalian Demam Berdarah Dengue di Indonesia*, K.K. RI, Dirjen Pengendalian Penyakit dan Penyehatan Lingkungan.

NTB, D.P., *PROFIL KESEHATAN PROVINSI NUSA TENGGARA BARAT 2019*. 2020, Dinas Kesehatan Provinsi Nusa Tenggara Barat: Mataram.

Ruri Trisasi , E.A., Riris Andono Ahmad, *Faktor risiko kematian akibat dengue di rumah sakit Sardjito Yogyakarta.* BKM Journal of Community Medicine and Public Health, 2018. **34**: p. 1-5.

Samir Bhatt, P.W.G., Oliver J Brady , Jane P Messina , Andrew W Farlow , Catherine L Moyes , John M Drake , John S Brownstein , Anne G Hoen , Osman Sankoh , Monica F Myers , Dylan B George , Thomas Jaenisch , GR William Wint , Cameron P Simmons , Thomas W Scott , Jeremy J Farrar , Simon I Hay, *The Global Distribution and Burden of Dengue.* Nature, 2013. **Nature**: p. 504–507.

WHO, *Comprehensive guidelines for prevention and control of dengue and dengue haemorrhagic fever*, R.a.e. edition, Editor. 2011, WHO Regional Office for South-East Asia: India. p. 17.

WHO. *Dengue and Severe Dengue*. 2020 [cited 2021 5 Maret]; Available from: https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue.