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DOI: [10.31965/infokes.Vol21Iss4.1382](https://doi.org/10.31965/infokes.Vol21Iss4.1382)Journal homepage: <http://jurnal.poltekkeskupang.ac.id/index.php/infokes>**RESEARCH****Open Access****Neutrophil-lymphocyte Ratio and Platelet-lymphocyte Ratio as Early Sign Plasma Leakage Process in Dengue Infection****Aisya Nailatul Ashma<sup>1a</sup>, Satrio Budi Susilo<sup>2b</sup>, Sri Marwanta<sup>3c</sup>, Dhani Redhono Harioputro<sup>4d\*</sup>**<sup>1</sup> Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Central Java, Indonesia<sup>2</sup> Department of Internal Medicine, Universitas Sebelas Maret, Moewardi Hospital, Surakarta, Central Java, Indonesia<sup>3</sup> Division of Hematology and Medical Oncology, Department of Internal Medicine, Universitas Sebelas Maret, Moewardi Hospital, Surakarta, Central Java, Indonesia<sup>4</sup> Division of Tropical Infection Disease, Department of Internal Medicine, Universitas Sebelas Maret, Moewardi Hospital, Surakarta, Central Java, Indonesia<sup>a</sup> Email address: [aisyaashma08@gmail.com](mailto:aisyaashma08@gmail.com)<sup>b</sup> Email address: [robertsatriyo@gmail.com](mailto:robertsatriyo@gmail.com)<sup>c</sup> Email address: [drdrmarwantasppdmkes@staff.uns.ac.id](mailto:drdrmarwantasppdmkes@staff.uns.ac.id)<sup>d</sup> Email address: [dhani\\_redhono@staff.uns.ac.id](mailto:dhani_redhono@staff.uns.ac.id)

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**Abstract**

Dengue hemorrhagic fever remains a global health concern, especially in tropical and subtropical regions, such as Indonesia. Plasma leakage is the main symptom of Dengue infection which be seen through a hemoconcentration. NLR and PLR are cost-effective and easily measurable indexes that help to predict signs of infection. This study aims to analyze the correlation of NLR and PLR as early sign on hemoconcentration in Dengue infection. This study was an analytical observational method with a cross-sectional design. The study was conducted at the inpatient infectious disease wards of Dr. Moewardi General Hospital and Sebelas Maret University Hospital. The data was statistically analyzed using bivariate and multivariate analysis. There were seventy subject which of male was more than female. The result of bivariate analysis showed a statistically significant correlation for NLR ( $p = 0,008$ ;  $r = 0,314$ ) and non-significant for PLR ( $p = 0,150$ ;  $r = 0,174$ ). Both NLR and PLR were positively correlated with hemoconcentration. The effect of NLR on hemoconcentration was significant. There was a positive correlation significant between NLR and hemoconcentration in Dengue infection.

**Keywords:** DHF, Plasma Leakage, Hemoconcentration, NLR, PLR.**\*Corresponding Author:**

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## 1. INTRODUCTION

Dengue hemorrhagic fever (DHF) is a disease caused by the dengue virus and carried by *Aedes aegypti* mosquitoes to transmit to human (Schaefer et al., 2022). This disease is still a global health problem, especially in tropical and subtropical regions with varying risks influenced by climate, social, and environmental parameters (Wu et al., 2022). Indonesia as one of the dengue-endemic tropical countries has a fluctuating number of cases and the distribution of its territory is expanding annually (Kementerian Kesehatan Republik Indonesia, 2017).

The spectrum of clinical manifestations of dengue infection progresses to undifferentiated fever, DF, DHF, and DSS (WHO, 2022). The main symptom distinguishing DHF from DF is plasma leakage during the critical phase (Kularatne & Dalugama, 2022; Wang et al., 2020). Dengue virus infection develops through three phases of the disease course, namely fever, critical, and recovery (WHO, 2022). The febrile phase occurs for three to seven days after infection with symptoms of high fever, generally accompanied by body aches and headaches (Kularatne & Dalugama, 2022). Patients may also experience hemorrhagic symptoms, such as a positive tourniquet test to spontaneous bleeding (Muller et al., 2017). At the end of the febrile phase, patients tend to develop hypovolemic shock due to plasma leakage (Wang et al., 2020).

Plasma leakage can be seen from a  $\geq 20\%$  increase in hematocrit or the discovery of ascites fluid or pleural effusion on ultrasound examination or thoracic imaging (Halstead, 2019; Pizarro-torres, 2016). Visualization by ultrasound is very sensitive and specific, but not always available especially in hospitals with limited resources (Suwanto et al., 2016). Plasma leakage can be seen from a 20% increase in hematocrit or hemoconcentration obtained from inexpensive examinations, but establishing baseline values is difficult to do in patients who arrive late (Rodrigo et al., 2021). In addition, in clinical practice, doctors often detect pleural effusion and/or ascites in patients with an increased hematocrit value of less than 20% (Suwanto et al., 2016). The use of uniform hematocrit limit values at all ages and genders, without standardization of *cutoff values* can have an adverse impact on DHF management (Anagha et al., 2018). The other assessments are needed to predict plasma leakage so that it can help clinicians in making informed decisions.

The signs of infection can be seen through neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) values as cost-effective and easily measurable biomarkers (Yang et al., 2020). NLR values present the immune response and prognosis of disease progression (Zahorec, 2021). PLR values present inflammatory status, activation of platelets, and aggregation of platelets (Uzun et al., 2017). PLR values have also been shown to be a better parameter than platelets or lymphocytes for predicting the development of systemic inflammation (Gasparyan et al., 2019). In the case of DHF, the NLR value has a significant correlated with the severity seen from the incidence of shock and bleeding manifestations (Koundinya et al., 2021). However, the clinical value of PLR is still rarely considered. Meanwhile, there have been no studies focused on either of them as a prognostic marker for patient's clinical conditions specifically. Based on this background, researchers will analyze the effect of NLR and PLR values on hemoconcentration in Dengue infection.

This study aimed to analyze the correlation of NLR and PLR values and hemoconcentration in DHF.

## 2. RESEARCH METHOD

This study was an observational analytic method with a cross-sectional design approach. The study was conducted in two location of the inpatient infection ward at Dr. Moewardi General Hospital and UNS Hospital with the research subjects, were adult DHF patients from

January 2022 to December 2022. Subjects were selected by simple random sampling based on inclusion criteria, were aged 18-60 years, had positive results on Ig M dengue serology examination, and fulfilled WHO criteria (trombocytopenia  $<100.000$  cells/mm<sup>3</sup>; Hct rise  $\geq 20\%$ ) and exclusion criteria were suffering from other infectious diseases, such as typhoid fever, pulmonary TB, and pneumonia, having a history of hematological diseases such as ITP and aplastic anemia, and forced discharge before they can be evaluated.

The research subjects were calculated using a single sample formula for the correlation test. The results of these calculations showed that the minimum number of subjects was 51 subjects. Subjects were added by 10% to avoid the possibility of subject dropout (incomplete data). Therefore, the minimum subjects required in this research are 55 subjects.

The independent variables were NLR, PLR. The Confounding variables were age and gender. The dependent variable was hemoconcentration. NLR was the result of dividing the number of neutrophils and lymphocytes (Liu et al., 2019). PLR was the result of dividing the number of platelets and lymphocytes (Kwon et al., 2012). Hemoconcentration was a hematocrit increase of 20% from the baseline hematocrit value (Sriatkhachorn, 2017). The research data was taken through laboratory examination results in medical records.

The analysis data used SPSS statistic 23 for Windows. The data were analyzed descriptively to obtain the characteristics of the study subjects, followed by bivariate analysis with the Spearman rho test and multivariate with the linear regression with a stepwise method. The ethical review in this study was in accordance with letter number 648/IV/HREC/2023 issued by Dr. Moewardi General Hospital.

### 3. RESULTS AND DISCUSSION

The population of subjects was adult patients aged 18-60 years with a diagnosis of DHF. The study subjects were taken from populations that had met the inclusion and exclusion criteria and were determined using simple random sampling techniques.

**Table 1.** Frequency of Characteristic Data.

Variable	Frequency (n)	Percentage (%)
Sex		
Male	36	51,4
Female	34	48,6
Hemoconcentration		
↑ Hct $\geq 20\%$	22	31,4
↑ Hct $< 20\%$	48	68,6
Day-fever		
< 3 day	8	11,4
$\geq 3-7$ day	58	82,9
>7 day	4	5,7
Hematological characteristics		
Leukopenia	47	67,1
Thrombocytopenia	63	90,0
Anemia	7	10,0

The result was obtained from 70 research subjects of DHF patients (Table 1). As many as 51,4% of the subjects were male and 48,6% were female. Among them, as many as 31,4% of subjects were DHF patients who experienced plasma leakage during hospitalization which could be characterized by a  $\geq 20\%$  increase in hematocrit. Based on the onset of fever when coming to the hospital, the highest number was obtained, namely 82,9% of patients who came during fever day 3 to day 7. Based on hematological characteristics, 67,1% of subjects had leukopenia, 90% of subjects had thrombocytopenia, and 10% of subjects had anemia.

**Table 2.** The Descriptive of Characteristics Data.

Variable	Median (Range)
Age	25,50 (18-58)
Length of Stay	5 (2-9)
NLR	2,43 (0,31-9,52)
PLR	94,89 (13,16-592,06)
Hemoconcentration	13,33 (2,27-48,00)

The characteristics of data descriptively (Table 2) found that the median age of subjects were 25,5 years, length of hospitalization 5 days, NLR 2,43, PLR 94,89, and hemoconcentration 13,33%. The hemoconcentration values of subjects were between a minimum value of 2,27% and a maximum of 48%.

**Table 3.** The Results of Normality Test.

Variable	df	p-value
NLR	70	0,001
PLR	70	0,000
Hemoconcentration	70	0,009

The normality test is carried out to determine the distribution of each variable whether normal or not and as a determinant of data processing techniques (parametric tests or non-parametric tests). The normality test in this study used the Kolmogorov-Smirnov Normality Test because the sample size obtained exceeded 50. The variable is showed to be normally distributed if  $p > 0,05$ . Based on the normality test on SPSS 23.0, data variables of this study were not normally distributed.

**Table 4.** The Results of Bivariate Analysis.

Variable	r	p
NLR and Hemoconcentration	0,314	0,008
PLR and Hemoconcentration	0,174	0,150

Data researchers were not normally distributed, so the analysis bivariate used the Spearman Correlation Test. There was a significant relationship between NLR and hemoconcentration in DHF patients because the p-value was  $< 0,05$ . PLR value had a  $p > 0,05$  value so there was no significant relationship to hemoconcentration. The correlation value of each variable was NLR ( $r = 0,314$ ), and PLR ( $r = 0,174$ ). NLR and PLR values were positively correlated to hemoconcentration. This means that the higher of NLR and PLR values, so the higher of hemoconcentration value in dengue infection.

**Table 5.** The Results of Multivariate Analysis.

Variable	B	P
NLR	1,782	0,001
PLR	-0,133	0,295

The results of linear regression with a stepwise method (Table 5) showed that the independent variable had a significant effect individually on the dependent variable is NLR

with  $p = 0,001$  ( $p < 0,05$ ). The PLR variable did not have a significant effect on hemoconcentration. The magnitude of the influence can be seen from the R-value of NLR that was 0,385. From this output, a coefficient of determination (R-square) of 0,149 is also obtained which means that the effect of the NLR value on hemoconcentration was 14,9% with a multivariate equation, namely:  $Y = 9,412 + 1,782X$ .

## DISCUSSION

Plasma leakage is the main clinical sign of DHF which can be seen from an increase in hematocrit level  $\geq 20\%$  from the baseline value, also known as hemoconcentration condition (Kularatne & Dalugama, 2022). This study was known that as many as 22 (31,4%) subjects experienced DHF (with increased hematocrit  $\geq 20\%$ ), while 48 (68,6%) subjects did not experience hemoconcentration during the critical phase. This percentage is not much different from previous studies. It was stated that 37 out of 75 subjects (49%) experienced an increase in hematocrit  $\geq 20\%$  at Dr. Soetomo Regional General Hospital. The study was a retrospective study using medical records (Rizaliansyah et al., 2017). Plasma leakage and bleeding are associated with dengue prognosis and mortality. This results from disease pathogenesis through cytokine storms and antibody responses in vascular endothelial cells and hemostatic abnormalities after DENV infection (Talukdar et al., 2021). The hematological parameters of *dengue virus* infection fluctuate during febrile days, particularly on days 3 to 8. It starts with progressive leukopenia followed by thrombocytopenia and hemoconcentration due to plasma leakage (Chaloemwong et al., 2018). The hematological characteristics in this study were 67,1% of subjects had leukopenia, 90% of subjects had thrombocytopenia, and 10% of subjects had anemia.

The Correlation between NLR and hemoconcentration in DHF. The amount of NLR value is influenced by the number of neutrophils and lymphocytes. At the beginning of infection, there is an increase in the percentage of neutrophils so that the NLR value becomes higher. Then, during the acute to critical febrile phase, there will be an increase in lymphocytes due to reactive lymphocytosis and reversal of NLR values. It occurs on fever days 6 to 9 (Chaloemwong et al., 2018). Viral infection induces lymphocyte activation and antibody secretion. The immune defenses against infection depend on T cells than on antibodies. The cytotoxic T cells play an important role in the clearance of virus-infected cells. The cell will secrete several cytokines, such as IFN- $\gamma$  and TNF. The lymphocytosis causes a decrease in NLR value (Zhu et al., 2013). TNF- $\alpha$  cytokines will induce cell apoptosis, increase vascular permeability, and eventually cause bleeding. Elevated level of TNF- $\alpha$  is associated with increased vascular permeability in dengue infection patients (Jeewandara et al., 2015).

In this study, the median NLR value was 2,43 (0,31-9,52). According to Zahorec (2021), normal NLR values are in the range of 1-2. NLR values of  $>3$  and  $<0,7$  in adults is pathological. NLR values that are in the gray zone between 2,3-3,0 can serve as an early warning of pathological states such as cancer, atherosclerosis, infections, inflammation, psychiatric disorders, and stress (Zahorec, 2021). In COVID-19, high NLR values at hospital admission are associated with the risk of death. NLR values  $>3$  were not survived (Widjaya et al., 2023).

Based on the result of spearman rank test, it was stated that there is correlation significant between NLR ( $p=0,008$ ) and hemoconcentration in DHF with a positive correlation and a weak correlation level ( $r = 0,314$ ). In the multivariate analysis, there are significant effect of 14,9%. These results are different from the previous study. The decrease in NLR is significantly related to the severity of DHF, seen from the manifestations of bleeding and shock. This study used hematology data on the 6th fever day and Chi-square Test (Koundinya et al., 2021). A result mismatch occurs due to a difference in NLR data retrieval time. NLR is taken at the beginning of hospital admission with varying fever onset. The onset of fever is most likely to enter the hospital on the 3rd to – 7th day.

The Correlation between PLR and Hemoconcentration in DHF. The decrease of platelet values is due to various mechanisms that occur during viral infections. Generally, the decrease is caused by bone marrow suppression, platelet destruction, and platelet dysfunction (Tasya, Rahmayanti & Fitriangga, 2022). Plasma leakage that marks dengue events is thought to be related to platelet activation, release of inflammatory mediators, and endothelial cells infected with virus (Nascimento et al., 2014; Tasya, Rahmayanti & Fitriangga, 2022). T lymphocytes are the main immune cells active during DHF. CD8<sup>+</sup> T cells secrete cytokines that alter endothelial cells and cause plasma leakage resulting in DHF and DSS (Bhatt et al., 2021). An increase in lymphocytes associated with a decrease in platelet count can lead to increased bleeding complications in DHF patients (Clarice et al., 2019). The decrease in platelets occurs from the 3rd to the 10th day (the lowest on the 6th day), while the increase in lymphocytes can be found on the 5th to 9th day (the highest on the 7th day) (Chaloemwong et al., 2018).

In this study, the median PLR value was 94,89 (13,16-592,06). Normal PLR in men is in the range of 36,63-149,13 and women 43,36-172,68 (Wu et al., 2019). DHF patients have low PLR values due to a decrease in platelet count. Platelets infected with dengue virus experience mitochondrial dysfunction that causes cell death. The lowest average PLR score, which was  $78,1 \pm 44,2$  (Rini et al., 2020). This study found no significant relationship between PLR values and hemoconcentration in DHF patients ( $p=0,150$ ). The previous study have shown that there is no statistically significant relationship between PLR and dengue infection at Syarif Muhamad Alkadrie Hospital. The study used a cross-sectional approach with secondary data in the form of medical records and analyzed with a chi-square test. Hematology data was taken on the third day of fever, where it is still unable to predict the incidence of plasma leakage in dengue cases. (Tasya, Rahmayanti & Fitriangga, 2022). The insignificance in PLR results is thought to be due to data collection time where in this study, the onset of fever in hospital admission varies and is mostly from the third day to the seventh day. On that day, platelets and lymphocytes just begin to change.

There are still a few of study that discuss the relationship between PLR and DHF severity. The PLR value can be utilized for monitoring disease and treatment response which is not only evaluated at one point in time, but can be also utilized by monitoring within a period (Meng et al., 2016). A drastic increase in PLR in COVID-19 can indicate the severity of inflammation. The greater the change in PLR, the more severe the cytokine storm occurs and the worse the patient's prognosis (Qu et al., 2020).

#### 4. CONCLUSION

There was a significant correlation between NLR value and hemoconcentration in DHF patients, with a positive correlation which means that increased value of NLR, so increased level of hemoconcentration. There is no significant correlation between PLR values and hemoconcentration in Dengue infection, with a positive correlation which means that increased value of PLR, so increased level of hemoconcentration. With the research, It is hoped that NLR can be used as an early detection of plasma leakage in dengue infection.

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