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The Relation between Neutrophil Lymphocyte Count Ratio (NLCR) and Dengue Infection Grade of Severity in Adult Patients in RS Muhammadiyah Ahmad Dahlan Kediri in January 2019

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ABSTRACT
In Indonesia, dengue viral infection is one of the problems of public health that is increasing in the amount of people infected and the spread of the disease. Platelet and hematocrit are used to be the indicators to determine the progress of the disease, but the count of leucocyte is sometimes less concerned. It is known that approximately 80% of the leucocytes are neutrophils and lymphocytes. Therefore, the purpose of this study was to determine the relation between neutrophil lymphocyte count ratio (NLCR) and dengue infection grade of severity in adult patients in RS Muhammadiyah Ahmad Dahlan Kediri in January 2019. This study is an analytical observational research with cross-sectional design. The subjects of this study were adult patients (14 years old and above) infected by dengue virus, that had fulfilled the inclusive criteria and the exclusive criteria. The data used in this study was secondary data from the medical record of the patients who suffered from dengue infection in RS Muhammadiyah Ahmad Dahlan Kediri in January 2019. Then the data was analyzed by Spearman's test to know the relation between neutrophil lymphocyte count ratio (NLCR) and dengue infection grade severity in adult patients. The result of Spearman's test showed that p value = 0.000 ($p < 0.05$) and the result of contingency coefficient test was -0.733. There is a significant relation between NLCR and dengue infection severity index in adult patients. The lower the NLCR, the dengue infection grade will be more severe.

Keywords: NLCR, Dengue Viral Infection, Dengue Hemorrhagic Fever, Severity

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INTRODUCTION

In Indonesia, Dengue Hemorrhagic Fever (DHF) is one of the diseases that continue to raise the number of incidents and widen the spread over the country. DHF is a mosquito-borne viral disease that usually infects children and teenagers under 15 years old, but it also infects adults in general (Kementrian Kesehatan Republik Indonesia, 2018).

Total incidents of DHF in Indonesia happened on 2017 was 68,407 cases. The province with the highest incidents happened in Java Island was in West Java with 10,016 cases. The second position was East Java with 7,838 cases (Kementrian Kesehatan Republik Indonesia, 2018).

Kediri District Health Office reported that in 2018, there was a total of 215 DHF cases, and among those, there was 1 death case (Dinas Kesehatan Kota Kediri, 2019). The latest report in 2019 in Kediri, there were 185 cases from January through May 2019, 2 deaths were reported (Dinas Kesehatan Kota Kediri, 2019).

Dengue is a mosquito-borne viral infection transmitted by *Aedes spp.* mosquitoes. Dengue virus is from Flaviviridae family, it has 4 serotypes: DEN-1, DEN-2, DEN-3, and DEN-4. Clinically, patients infected by dengue virus disease development are differentiated by 3 phases, which are febrile phase, critical phase, and recovery phase. According to the severity of the infection, WHO (1997) defined the severity grade into Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF) with grade I, II, III, and IV.

The indicator that shows the development of the disease besides the clinical findings is complete blood count (CBC). WHO criteria (2011) defined that some components of CBC like leucocytes, platelets, and hematocrits are important for figuring out the clinical development of dengue. Commonly, platelet count and hematocrit are used as the indicator of the development of dengue infection, while in the other hand leucocyte count is less concerned (Risniati et al, 2011). Neutrophils and lymphocytes are 80% of the leucocytes and have the active role as body response to inflammation and infection so that immune response can be drawn from the proportion of those 2 cell types (Gurol et al, 2015).

The latest researches have used the neutrophil and lymphocyte count ratio (NLCR) as a marker to differentiate between bacterial infections and viral infections which the cut off is 6.2 (Holub et al, 2011). Dengue severity grade is also known that it is related to the inflammation occurred on dengue infection because of the exaggerating response of the immune system (Irmayanti et al, 2017).

From the problems mentioned above, researcher wants to know the relation between NLCR and dengue infection grade of severity in RS Muhammadiyah Ahmad Dahlan Kota Kediri in period January 2019.

METHODS

This study is an analytical observational research with cross-sectional design. The population of this study were adult patients (14 years old and above) infected by dengue virus in RS Muhammadiyah Ahmad Dahlan Kediri in January 2019 and *total sampling* technique was used to select the subjects. The study contains of 2 variables, NLCR as the dependent variable and dengue grade of severity as the independent variable. The data used in this study was secondary data from the medical record of the patients who suffered from dengue infection in RS Muhammadiyah Ahmad Dahlan Kediri in January 2019.

There were inclusive criteria and exclusive criteria made for the subjects. The inclusive criteria are patients who hospitalized because of dengue viral infection, ≥ 14 years old, the result of the blood test used was the examination in 3rd or 4th day of fever, the patient has complete medical record status. Meanwhile, the exclusive criteria are patient who has dual

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infection beside the dengue viral infection, < 14 years old, incomplete medical record status. All subjects must fulfill the inclusive and exclusive criteria.
Then, the data was analyzed by Kolmogorov smirnov to determine the data distribution. Because the distribution of the data was abnormal, the Spearman's test was used to know the relation between neutrophil lymphocyte count ratio (NLCR) and dengue infection severity grade in adult patients with SPSS Program.

RESULTS

Total subjects in this study were 76 patients, consist of 43 men (56.6%) and 33 women (43.4%). Patients infected by dengue virus mostly in the age of 17 to 25 years old. Based on patient's length of stay in the hospital, 47 patients (61.9%) hospitalized for ≤ 4 days while 29 patients (39.1%) hospitalized for > 4 days. According to the dengue severity grade, 54 patients (71.1%) suffered from Dengue Hemorrhagic Fever (DHF) grade I, 14 patients (18.4%) suffered from DHF grade II, and 8 patients (10.5%) suffered from DHF grade III.

Table 1. Subject characteristic based on gender

Gender	Frequency (n)	Percentage (%)
Male	43	56.6
Female	33	43.4
Total	76	100

Table 2. Subject characteristic based on age group

Age Group	Frequency (n)	Percentage (%)
< 17 years old	19	25
17 – 25 years old	36	47.4
26 – 35 years old	14	18.4
36 – 45 years old	5	6.6
> 45 years old	2	2.6
Total	76	100

Table 3. Subject characteristic based on length of stay in hospital

Length of stay	Frequency (n)	Percentage (%)
≤ 4 days	47	61.9
> 4 days	29	39.1
Total	76	100

Table 4. Subject characteristic based on DHF severity grade

DHF Severity Grade	Frequency (n)	Percentage (%)
Grade I	54	71.1
Grade II	14	18.4
Grade III	8	10.5
Grade IV	0	0
Total	76	100

The result of Spearman's test showed that p value = 0.000 and the result of contingency coefficient test was -0.733. Because p < 0.05 means there is significant relation between NLCR and dengue severity grade. C > 0.5 shows that there is a strong relation between 2

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variables of the research. The negative value means there is opposite direction between 2 variables, the lower the NLCR, the higher severity grade of dengue viral infection.

DISCUSSION

Dengue infection commonly causes leucopenia. Leucopenia is a marker which indicates that the febris will go down and the patient will enter the critical phase. In critical phase, the leucocyte count will decline (< 5000 cells/mm^3) and neutrophil and lymphocyte count ratio will change where neutrophil will decrease so that neutrophil count is less than lymphocytes. That conditions will be the predictor of critical phase in which plasma leakage occurs. The change happens before thrombocytopenia or raising hematocrit occurs. Relative lymphocytosis with increasing atypical lymphocytosis is usually found later in the febrile phase or in the recovery phase (WHO, 2011).

The neutropenia condition is caused by the virus infection which causes the neutrophil to apoptosis because the apoptosis rate of neutrophils has a positive correlation with disease severity grade thus it supports protective role of neutrophil in antiviral response (Galani, 2015). That statement is also supported by Candra (2010) who stated that dengue severity grade has a close relation with the exaggerating inflammation occurred because of excessive immune response.

Based on this research, there is a significant relation between NLCR and dengue severity grade in adults in RS Muhammadiyah Ahmad Dahlan Kota Kediri in January 2019. This result corresponds with Irmayanti et al's statement (2017) that showed there was a relation between NLCR and dengue infection ($p < 0.05$). The mean NLCR on DHF grade I is 2.19 and DHF grade II is 0.80 so that the lower the NLCR, the dengue infection will be more severe.

Another cross sectional research done in RSUP Dr. Kariadi and RSND Semarang showed that there was a statistically significant difference between NLCR and DF and DHF. This research showed that NLCR in DHF group is lower (mean NLCR = 0.55) than DF group (mena NLCR = 1.23) (Yuntoharjo et al, 2018).

Karla et al's research (2015) showed a contrast result from this research that concluded there was no significant relation between NLCR and dengue severity grade ($p = 0.63$). From her explanation, things that could affect the result were quality and type of the tools used, laboratory staff's examination skill and taking blood samples on different days of fever (2^{nd} – 7^{th} day of fever). In the other hand though, this research used samples from 3^{rd} and 4^{th} day of fever.

CONCLUSION

There is a significant relation between NLCR and dengue infection severity grade in adult patients in RS Muhammadiyah Ahmad Dahlan Kediri in January 2019. The lower the NLCR, the dengue infection grade will be more severe.

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