



RELATIONSHIP BETWEEN NEUTROPHIL-LYMPHOCYTE RATIO AND CLINICAL SPECTRUM OF COVID-19 PATIENTS AT RSUD TUGUREJO SEMARANG

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ABSTRACT

Background: Coronavirus Disease 2019 (COVID-19) is an infectious respiratory disease caused by an infection novel coronavirus called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). COVID-19 patients have different clinical spectrums, depending on individual susceptibility and virus's ability to infect. One of the parameters, Neutrophil to Lymphocyte Ratio (NLR), can be used for screening, monitoring, and evaluating COVID-19 patients. **Objective:** This study aims to determine whether there is a relationship between NLR and the clinical spectrum of COVID-19 patients at Tugurejo Hospital, Semarang. **Methods:** The size of sample are 99 COVID-19 patients fit into the inclusion criteria carried out by data from medical records. NLR was the independent variable that measured by neutrophil count divided lymphocyte count and clinical spectrum was the dependent variable which contain a mild, moderate and severe severity. This study used cross sectional design and consecutive sampling. Data analysis to decide whether there is a relationship for both variable used chi square test as a bivariate analysis. **Results:** The subjects of this study were aged 19 - 91 years. Most of the patients severity was moderate (49.5%) and the average of NLR result was 7.5456. On Chi Square test found the result of p-value is 0.045 (<0.05) between neutrophil lymphocyte ratio with the clinical spectrum of COVID-19 patients. Which meant that there was significant positive relationship between both variables. **Conclusion:** There is significant positive relationship between neutrophil lymphocyte ratio with clinical spectrum of COVID-19 patients at Tugurejo Hospital Semarang.

Keywords: *Clinical Spectrum of COVID-19 Patients, COVID-19, Neutrophil, Lymphocyte, Neutrophil Lymphocyte Ratio.*

INTRODUCTION

At the end of December 2019, a new coronavirus appeared, which spread very quickly. The virus is Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), works by infecting the human respiratory tract causing Coronavirus Disease-2019 (COVID-19), which has spread widely throughout countries including Indonesia.¹ The number of COVID-19 in Indonesia is quite high. As of March 30 2022, there were 5,847,900 confirmed cases and 151,414 deaths place Indonesia sixth out of all countries in Asia.²⁻³ According to data as of June 12th, 2022, Central Java province reached 627,783 positive cases of COVID-19, while the death cases totalled 33,198. This number of death cases puts Central Java in the first place with the highest rate compared to other provinces.⁴⁻⁵

The new coronavirus variant is known to come from the *Betacoronavirus* type.⁶ Patients infected with this virus can have symptoms that are not typical, resembling other diseases, and cause disturbances in various organ systems. So it is not easy to diagnose someone who has COVID-19 without do some supporting examinations.⁷

The diagnosis process requires a supporting examination, namely RT-qPCR, which is the gold standard test for diagnosing COVID-19. However, the availability of laboratory facilities and human resources to carry out these tests is still limited and not evenly distributed in several regions. This situation can affect the time needed to confirm a COVID-19 patient, so there can be delays in the diagnosis and management of patients.⁸ Therefore, other supporting tests are needed to help screen the condition of COVID-19 patients.⁹

One of the supporting examinations that can be used is a haematological examination according to recommendations from the Ministry of Health of the Republic of Indonesia for screening, monitoring and evaluating the patient's condition.¹⁰ One of the haematological test is the neutrophil lymphocyte ratio which is obtained by calculating neutrophils absolute divided lymphocytes absolute. It is known from the previous studies that combination of these two haematological profiles and the result of NLR has increased, indicating an inapplicability the response of body's immune.¹¹



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A significant inflammatory response can be identified by an elevated neutrophil-lymphocyte ratio. This can cause an imbalance in body's immune response, where the number of neutrophils increases as an inflammatory response infection and a decrease in lymphocytes indicates an inflammatory process.¹¹⁻¹³

The NLR examination can be assessed when the patient is admitted to the hospital for screening, classifying and evaluating the patient's prognosis to determine the initial phase of the COVID-19 disease course. This is done to help medical personnel make early detection and earlier management of patients to achieve better outcomes.^{8,14-15} This study to determine whether there is a relationship between neutrophil lymphocyte ratios with clinical spectrum of COVID-19 patients at Tugurejo Hospital, Semarang.

METHODS

An analytical observational study and a cross-sectional research design characterize this quantitative research type. The collected samples of 99 patients were taken through consecutive sampling techniques regarding inclusion and exclusion criteria. The inclusion criteria all patient confirmed to have COVID-19 using PCR from June 2021 to June 2022 had an NLR examination from complete blood count test at the time of admission to the hospital, aged >18 years. While patients with COVID-19 who were pregnant were excluded.

The neutrophil lymphocyte ratio calculated using absolute neutrophil count divided by lymphocyte count served as the studies independent variable. NLR result and the severity of COVID-19 patients divided into mild, moderate and severe seen from clinical manifestation and physical examination served as the studies dependent variable. The Chi-Square test is utilized in this study's bivariate analysis to assess the relationship between the two variables and using a descriptive correlation analysis based on references. The frequency distribution and percentage of each variable analyzed are narratively described in univariate.

RESULTS

The kind of data used was secondary information collected by reviewing the medical records of COVID-19 patients.

Univariate Analysis

Table 1. Frequency Distribution of COVID-19 Patients Characteristic

Variable	Frequency	%
Neutrophil Lymphocyte Ratio (NLR)		
Low Risk (<3.13)	23	23,2
High Risk (≥3,13)	76	76,8
Clinical Spectrum		
Mild	21	21,2
Moderate	49	49,5
Severe	29	29,3
Gender		
Male	53	53,5
Female	46	46,5
Age (years)		
19 – 25	12	12,1
26 – 35	16	16,2
36 – 45	17	17,2
46 – 55	21	21,2
56 – 65	19	19,2
>65	14	14,1

In table 1 the characteristics of the neutrophil lymphocyte ratio of patients are categorized as low risk (<3.13) and high risk (≥3.13). Neutrophil lymphocyte ratio results ranged from 1.01 - 43.91 with average 7,5456 and most of the patients had NLR ≥3.13 or were at high risk with total 76 (76,8%). Most patients (49,5%) had moderate symptoms, which were classified on the clinical criteria as mild, moderate, and severe. Male patients make up 53.5% of the total, while female patients make up 46.5% of the total. The findings revealed that COVID-19 patients ages ranged from 19 to 91. The age was divided into six categories for this study 21 (21.2%) most of the patients fell into the 46–55 age range.

The distribution of COVID-19 patients with comorbidities and without comorbidities is seen in Table 2. As many as 59 (59.6%) of the COVID-19 patients had comorbid conditions, with hypertension being the most prevalent (at 12.1%).



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Table 2. Frequency Distribution of COVID-19 Patients Characteristic

Variable	Frequency	%
Comorbidity History		
1 Comorbid		
Hypertension	12	12,1
Diabetes Mellitus Type 2	10	10,1
Obesity	7	7,1
HIV/AIDS	2	2,0
Chronic Obstructive Pulmonary Disease	1	1,0
Upper Respiratory Tract Infection	1	1,0
Hemorrhagic Stroke	1	1,0
Chronic Kidney Disease	1	1,0
Renal Insufficiency	1	1,0
Breast Cancer	1	1,0
Arrhythmia	1	1,0
Ischemic Heart Disease	1	1,0
>1 Comorbid		
DM Type 2 & Hypertension	4	4,0
DM Type 2 & Ischemic Heart Disease	1	1,0
Hypertension & Coagulopathy	1	1,0
Non Hemorrhagic Stroke & Neuropathy DM	1	1,0
Hypertension & Obesity	1	1,0
Acute Decompensated Heart Failure, Ischemic Heart Disease, Congestive Heart Failure	1	1,0
STEMI Inferior, Paroxysmal Atrial Fibrillation, Breast Cancer	1	1,0
DM Type 2, Hypertension, Dyslipidemia	1	1,0
Hypertension, Ischemic Heart Disease, Hypertensive Heart Disease	1	1,0
DM Type 2, Hypertension, Congestive Heart Failure	1	1,0
DM Type 2, Coagulopathy	1	1,0
Chronic Kidney Disease, Hepatitis B	1	1,0
Hypertension, Ischemic Heart Disease	1	1,0
DM Type 2, Chronic Kidney Disease	1	1,0
DM Type 2, Hypertension, Chronic Kidney Disease, Atrial Fibrillation	1	1,0
Hypertension, Chronic Kidney Disease	1	1,0
Without Comorbid	40	40,4

Bivariate Analysis

Table 3. Relationship between Neutrophil Lymphocyte Ratio and Clinical Spectrum of COVID-19 Patients

NLR Category	Clinical Spectrum			p
	Mild	Moderate	Severe	
Low Risk	9 (39,1%)	10 (43,5%)	4 (17,4%)	0,0
High Risk	12 (15,8%)	39 (51,3%)	25 (32,9%)	45

Table 3 shows the relationship between NLR and the severity of COVID 19. This research shows that 51.3% of COVID patients with a moderate degree had high-risk NLR. The analysis result is a p-value of 0.045, which means that the p-value is lower than the significance level (<0.05), indicating a significant relationship between NLR and severity of COVID-19 patients.

RESULTS

The neutrophil-lymphocyte ratio study revealed that most samples had NLR values ≥ 3.13 . According to Liu, et al., a study classified neutrophil lymphocyte ratio as low Risk (<3.13) and high Risk (≥ 3.13). The majority of patients with NLR ≥ 3.13 are over 50 years old.¹⁶ The imbalanced immunological response from neutrophilia and lymphopenia accounts for the high neutrophil-lymphocyte ratio. The imbalanced immunological response from neutrophilia and lymphopenia accounts for the high neutrophil-lymphocyte ratio suggesting a broad inflammatory reaction compromises the immune system.¹²

Patients typically fall into a moderate clinical spectrum. Lower respiratory tract disorders like pneumonia characterized by fever, shortness of breath, coughing, rapid breathing but not severe pneumonia, and SpO₂ 94% are characteristics of the moderate clinical spectrum.¹⁷⁻¹⁸ Because some immune systems are more susceptible to infection by the virus than others, clinical outcomes can vary between individuals.¹⁸

The most common age group is between the ages of 46 and 55. They can transmit COVID-19 easily because they are still in the productive age group with high mobility, and are active outside the home. As to guidelines from the Republic of Indonesia's Ministry of Health, the majority of COVID-19 cases in Indonesia affect people between the ages of 45 and 55.¹⁹



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The male sex has a higher prevalence of COVID-19 than the female sex. Men are more likely than women to smoke and have heart and lung illnesses, which explains this, which makes it simple for the virus to bind to specific Angiotensin Converting Enzyme 2 receptors. As a result of this mechanism, ACE-2 expression will increase.²⁰

Comorbidity with each pathophysiology can oppose the patient's clinical condition. Most COVID-19 patients have comorbidities, with the highest comorbidity being hypertension. Previous research by Kadek, et. al., found that the most common comorbidity was hypertension in COVID-19 patients.²¹ Hypertension is the most common cardiovascular comorbidity and increases the risk of death.²² Susceptibility to SARS-CoV-2 later will lead to aggravation and severity of COVID-19 infection. ACE-2, a virus-specific receptor by endothelial cells, will be expressed, causing vascular endothelial dysfunction.²³

There was a significantly correlated between NLR and severity in COVID-19 patients. Earlier studies by Sintoro, et al., found a substantial correlation between the clinical spectrum of COVID-19 and NLR, with the severity increasing as the NLR rose.²⁴ An elevated neutrophil lymphocyte ratio will be the outcome of elevated neutrophils and decreased lymphocytes.¹¹

It is known that when SARS-CoV-2 enters the respiratory tract, it will go to the alveolar epithelial cells and attach to its specific receptor, namely Angiotensin Converting Enzyme 2 (ACE-2). Furthermore, the virus will undergo several processes that release new viruses from replication into the body's cells. The presence of the virus will be responded to by the virus-specific immune system (cellular immunity) by removing lymphocytes. Helper T cell lymphocytes (CD4+) play a role in producing virus-specific antibodies and together with endothelial cells will release viral inflammatory factors which will trigger the release of inflammatory cells such as neutrophils. Cytotoxic T lymphocytes (CD8+) work directly to kill viruses that infect the body.²⁵

Increased levels of inflammatory factor expenditure cause the lymphocyte population to decrease along with the severity of the patient's infection. Lymphopenia that occurs in COVID-19 patients is also related to neutrophilia. The increase in

neutrophils occurs because the lack of lymphocytes will facilitate infection from other microbes.²⁴

The limitation of this study is that it does not discuss other supporting tests in COVID-19 patients such as D-Dimer, IL-6 and CRP. The data analysis carried out can only determine the relationship between the two variables, not how strong the relationship between these variables is.

CONCLUSION

Most of the COVID-19 patients who were hospitalized from June 2021 to June 2022 had a neutrophil lymphocyte ratio ≥ 3.13 (High Risk). Most of the clinical spectrums of COVID-19 patients are moderate clinical spectrums. There is a relationship between the neutrophil lymphocyte ratio and the clinical spectrum of patients infected with COVID-19.

ETHICAL APPROVAL

This research was conducted following the approval of an Ethical Clearance that was considered ethically permissible by Komisi Etik Penelitian Kesehatan (KEPK) RSUD Tugurejo Provinsi Jawa Tengah No. 087/KEPK.EC/X/2022 dated October 17, 2022.

CONFLICTS OF INTEREST

The authors declare there is no conflict of interest in this study.

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AUTHOR CONTRIBUTIONS

Conceptualization, Shafa Salina; methodology, Shafa Salina; writing-drafting, Shafa Salina, Yekti Hediningsih and Andra Novitasari; supervision, Yekti Hediningsih and Andra Novitasari

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