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Increase in Neutrophil Lymphocyte Ratio in COVID-19 Patients Based on Symptom Severity

(Peningkatan Nilai Rasio Neutrofil Limfosit Pada Pasien COVID-19 Berdasarkan Tingkat Keparahan Gejala)

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Abstrak

Rasio Neutrofil limfosit (NLR) merupakan salah satu indikator terhadap adanya respon inflamasi sistematis yang secara luas digunakan sebagai penentu prognosis dari pasien dengan pneumonia karena virus. Parameter rasio neutrofil limfosit dihitung dengan cara membandingkan jumlah neutrofil dan jumlah limfosit. Pasien COVID-19 yang parah dan yang tidak survive ditemukan hasil nilai rasio neutrofil limfosit yang lebih tinggi dibandingkan dengan pasien dengan prognosis yang ringan. Penelitian ini bertujuan untuk melihat gambaran nilai rasio neutrofil limfosit pada pasien COVID-19 berdasarkan tingkat keparahan gejala. Metode Penelitian ini menggunakan metode deskriptif. Nilai rata-rata rasio neutrofil limfosit (NLR) tinggi pada pasien COVID-19 terjadi pada kategori berat (6,12) dan kritis (10,78). Nilai rata-rata neutrofil tinggi (Neutrophilia) pada pasien COVID-19 terjadi pada kategori berat (76%) dan kritis (82%). Nilai rata-rata limfosit rendah (lymphocytopenia) pada pasien COVID-19 terjadi pada kategori berat 17% dan kritis 12%. Nilai NLR pada pasien dengan kategori berat memiliki peningkatan nilai NLR dua kali lipat dari nilai normal, sedangkan pada kategori kritis memiliki peningkatan nilai NLR tiga kali lipat dari nilai normal.

Kata kunci: Rasio neutrofil limfosit (NLR), COVID-19, Tingkat Keparahan Gejala

Abstract

The neutrophil lymphocyte ratio (NLR) is an indicator of the presence of a systemic inflammatory response. The neutrophil lymphocyte ratio parameter was calculated by comparing the number of neutrophils and the number of lymphocytes. Patients with severe COVID-19 who did not survive were found to have a higher neutrophil lymphocyte ratio compared to patients with a mild prognosis. This study uses a descriptive method, which aims to describe the value of the neutrophil lymphocyte ratio in COVID-19 patients based on the severity of symptoms. The average value of high neutrophil lymphocyte ratio (NLR) in COVID-19 patients occurred in the severe (6.12%) and critical (10.78%) categories. The average value of high neutrophils (Neutrophilia) in COVID-19 patients occurred in the severe (76%) and critical (82%) categories. The average value of low lymphocytes (lymphocytopenia) in COVID-19 patients occurred in the severe 17% and critical 12% category. The NLR value in patients with the severe category had an increase in the NLR value twice the normal value, while in the critical category had an increase in the NLR value three times the normal value.

Keywords: Neutrophil lymphocyte ratio (NLR), COVID-19, symptom severity

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INTRODUCTION

Coronaviruses are a large family of viruses that cause disease in animals and humans. Several coronaviruses are known to cause respiratory infections in humans ranging from the common cold, to more severe diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). COVID-19 is transmitted through droplets that come out when an infected person coughs, sneezes or talks [1]. In July 2023, WHO reported 21 new cases of COVID-19 out of a total of 6,812,987 cases [2]. Meanwhile, data from the Yogyakarta Provincial Health Service until the 34th week of August 2024 showed that no new cases were found from a total of 128 confirmed positive cases with a death toll of 5 people [3].

Coronaviruses are zoonotic, which means there is a possibility that they were transmitted from animals to humans. The incubation period for COVID-19 is 5-6 days, with a range between 1 and 14 days [4]. The highest risk of transmission occurs in the first days of illness because it is caused by a high concentration of virus in secretions. Transmission of COVID-19 can be through direct contact with infected people and indirect contact with surfaces or objects used on infected people. Transmission is mainly through droplets or contact with contaminated objects [5]. The clinical spectrum of COVID-19 varies from asymptomatic to severe symptomatic. Mild clinical manifestations include fever, cough, shortness of breath, headache, sore throat, and rhinorrhea, while severe clinical manifestations include severe pneumonia, sepsis, septic shock, Acute Respiratory Distress Syndrome (ARDS), and multiple organ failure syndrome. [1].

Hematology examination is one of the supporting diagnostic examinations to assess the severity of the disease and predict the risk in COVID-19 patients. Neutrophil lymphocyte ratio is an indicator of the presence of a systemic inflammatory response which is widely used as a determinant of the prognosis of patients with viral pneumonia [6]. The neutrophil lymphocyte ratio parameter is calculated by comparing the number of neutrophils and the number of lymphocytes.

Neutrophils are the main component of leukocytes that actively migrate towards the immune system or organs. Neutrophils release large amounts of Reactive Oxygen Species (ROS) which cause cell DNA damage resulting in the virus leaving the cell, then Antibody-Dependent Cell-Mediated Cell (ADCC) can kill the virus directly and trigger humoral immunity [7]. Lymphocytes are part of the adaptive immune response. The lymphocyte cell group is a derivative of lymphoid progenitor cells. Lymphocytes can mediate specific immune reactions against foreign molecules and can recognize these molecules (memory function) to deal with the next attack [8]. Lymphopenia accompanied by neutrophilia in COVID-19 patients may result from several mechanisms, including the recruitment of lymphocytes and monocytes from the bloodstream to the infection site, Activation-Induced Cell Death (AICD) of lymphocytes triggered by increased excretion of pro-apoptotic factors under the influence of IL-6, atrophy of lymphoid organs, and disrupted lymphocyte turnover. These factors may be linked to excessive activation and exhaustion of lymphocytes [9].

Neutrophil lymphocyte ratio is an indicator of the presence of a systemic inflammatory response which is widely used as a determinant of the prognosis of patients with viral pneumonia [6]. The neutrophil lymphocyte ratio parameter is calculated by comparing the number of neutrophils and the number of lymphocytes. Severe Covid 19 patients who did not survive were found to

have higher neutrophil lymphocyte ratio values compared to patients with a mild prognosis [10]. According to previous research, the results show that there is a strong relationship between the neutrophil lymphocyte ratio and the clinical grade of COVID-19. The increasing clinical degree of COVID-19 infection, the higher the neutrophil lymphocyte ratio value [11], so the focus of this study is to see the increase in the neutrophil lymphocyte ratio value in COVID-19 patients based on the severity of symptoms.

METHODS

This research is a descriptive analysis research with a cross-sectional approach. This research was conducted in 2023 by collecting secondary data in 2021.. The data used in this study were medical record data from 281 patients who met the inclusion criteria. The inclusion criteria are patients with confirmed COVID-19 with complete blood count data and undergoing hospitalization in July 2021 at the Panembahan Senopati Hospital, Bantul. Complete blood count data is obtained from the results of the hematology analyzer examination. The complete blood count data taken are the Neutrophils count and lymphocytes count parameters. Neutrophils count and lymphocytes count data are used as the basis for calculating the neutrophil lymphocyte ratio. NLR is measured by dividing the number of neutrophils by the number of lymphocytes [12]. The NLR value is categorized as normal if ≤ 3.13 and categorized as high if ≥ 3.13[13]. Meanwhile, the neutrophil value is categorized as Neutrophilia (high) if > 70% (normal value: 50%-70%) [14], for lymphocyte values it is categorized as lymphocytopenia (low) if < 20% (normal value 20%-40%)[15]. The severity of COVID-19 symptoms is divided into four categories, namely mild, moderate, severe and critical [16].

RESULTS AND DISCUSSION

Data from 281 COVID-19 patients that have been collected are then grouped by age and gender (table 1) to determine the characteristics of the most sufferers in COVID-19 patients. Based on table 1, the most sufferers of COVID-19 patients occurred at the age of 56-65 years (late elderly) 23% and in the female gender 54%.

Table 1. Characteristics of Confirmed COVID-19 Patients Based on Neutrophil Lymphocyte Ratio Values

Patient Characteristics	Frequency (%)	NLR Value	
		Normal (%)	>Normal (%)
Age (years)			
Toddler (0-5)	9 (3)	5 (56)	4 (44)
Children (5-11)	1 (1)	1 (100)	0 (0)
Early adolescence (12-16)	1 (1)	0 (0)	1 (100)
Late teens (17-25)	13 (5)	3 (23)	10 (77)
Early adulthood (26-35)	34 (12)	11 (32)	23 (68)
Late adulthood (36-45)	49 (17)	20 (41)	29 (59)
Early elderly (46-55)	54 (19)	11 (20)	43 (80)

Late elderly (56-65)	65 (23)	6 (9)	59 (91)
Seniors (>65)	55 (19)	23 (42)	32 (58)
Total	**281 (100)**	**80 (28)**	**201 (72)**
Gender			
Female	153 (54)	41 (27)	112 (73)
Male	128 (46)	38 (30)	90 (70)
Total	**281 (100)**	**79 (28)**	**202 (72)**

COVID-19 patient data is categorized into four categories, namely mild, moderate, severe, critical. These categories are distinguished based on the NLR value to see the abnormal number as a sign of inflammation. Based on table 2, 92% of COVID-19 patients in the critical category have NLR values above normal.

Table 2. NLR Value Based on Symptom Severity in COVID-19 Patients

Symptom Severity	**Frequency (%)**	**NLR Value**	
		Normal (%)	**>Normal (%)**
mild	20 (7)	20 (100)	0
moderate	34 (12)	32 (94)	2 (6)
severe	136 (48)	20 (15)	116 (85)
critical	91 (33)	7 (8)	84 (92)
Total	**281 (100)**	**79 (28)**	**202 (72)**

The average NLR value data can be seen in table 3. The average NLR value is used as a sign of inflammation in COVID-19 patients and how much the average NLR value increases compared to normal values (normal value ≤ 3.13). The largest increase from normal values occurred in patients with severe (6.12) and critical (10.78) categories. The highest NLR value of 93.00 occurred in the critical category.

Table 3. Average NLR Value in COVID-19 Patients

Symptom Severity	**NLR Value**			
	SD	**Average**	**Max**	**Min**
mild	0.49	1,39	1,93	0,42
moderate	0.49	2,50	3,65	1,50
severe	4.36	6,12	23,75	0,48
critical	10.65	10,78	93,00	1,18

The average data of neutrophil values can be seen in table 4. An increase in neutrophil values (Neutrophilia) from normal values (normal values 50% -70%) indicates resistance to viral infections. Neutrophils release large amounts of Reactive Oxygen Species (ROS) which cause damage to cell DNA which causes the virus to exit the cell, then Antibody-Dependent Cell-Mediated Cell (ADCC) can kill the virus directly and trigger humoral immunity. An increase in the number of neutrophils (Neutrophilia) occurs in patients with severe (76%) and critical (82%) categories.

Table 4. Neutrophil Values in COVID-19 Patients

Symptom Severity	**Neutrophil Value**			
	SD	**Average (%)**	**Max (%)**	**Min (%)**
mild	13.98	50	88	21
moderate	5.39	64	75	51
severe	10.00	76	97	32
critical	9.35	82	94	46

The average lymphocyte value data can be seen in table 5. Lymphocytes play a role in the immune system to fight viruses. A decrease in lymphocyte values (lymphocytopenia) from normal values (normal values 20%-40%) indicates fatigue from the lymphocyte response to COVID-19 virus infection. A decrease in the number of lymphocytes (lymphocytopenia) occurs in patients with severe (17%) and critical (12%) categories.

Table 5. Lymphocyte Values in COVID-19 Patients

Symptom Severity	**Lymphocyte Value**			
	SD	**Average (%)**	**Max (%)**	**Min (%)**
mild	11.87	39	69	26
moderate	4.05	29	38	20
severe	9.01	17	66	4
critical	8.00	12	39	1

This research was carried out at the Laboratory and Medical Records Unit of Panembahan Senopati Hospital by taking data from patients confirmed positive for COVID-19 who underwent hospitalization and complete blood count examinations in July 2021. The data obtained was 281 COVID-19 patients, 153 female patients (54%) and 128 (46%) male patients (table 1). Female patients have a higher number of cases, but other research shows that the majority of COVID-19 patients are men. This gender distribution is related to the greater prevalence of active smokers in men, this is thought to be due to the habit of smoking which can increase the expression of the

ACE2 receptor, where the ACE2 receptor is the infection receptor for the COVID-19 virus [17]. Based on gender, NLR values that were > normal were found mostly in women (112 patients (73%)) compared to men (90 patients (70%)).

In terms of age, the largest group of COVID-19 patients was found in the 56–65 age group, with 65 patients (23%), of whom 91% had an NLR higher than the normal range. This is in accordance with research conducted by Halil & Anwar [18] that older patients have NLR values > normal because there are changes in the immune system in the patient's body resulting in a gradual decline in immune function. Neutrophil lymphocyte ratio (NLR) is an indicator of the presence of an inflammatory response, used to determine the prognosis of patients with pneumonia caused by viruses. Elevated NLR may reflect an increased inflammatory process and is associated with a poor prognosis. NLR plays a role in monitoring immune and inflammatory responses in the body, so NLR monitoring is expected to provide insight into the treatment and prognosis of COVID-19 patients [19] [20].

Based on the data in table 2 severity levels of severe and critical symptoms have NLR values > normal. 116 (85%) patients had severe symptoms and 84 (92%) patients had critical symptoms with an average NLR value for severe symptoms of 6.12% and critical symptoms of 10.78% (table 3). Other studies also show that NLR > Normal occurs in the severe category at 34.9% and critical at 65.1% [6]. This shows that the more severe the patient's condition, the NLR value tends to increase. The increase in NLR values in COVID-19 patients was caused by an increase in the number of neutrophils and a decrease in the number of lymphocytes as a result of infection with the COVID-19 virus[21], [22].

The average neutrophil value in COVID-19 patients with mild and moderate severity had normal neutrophil values, while those with severe and critical symptoms had neutrophil values > normal, 76% with severe symptoms and 82% with critical symptoms (table 4). The average lymphocyte value in COVID-19 patients with mild and moderate severity had normal lymphocyte values, while those with severe and critical symptoms had < normal lymphocyte values, 17% with severe symptoms and 12% with critical symptoms (table 5). The results in this study show that there are differences in neutrophil, lymphocyte and NLR values in COVID-19 patients with mild, moderate, severe and critical symptom severity, this is in accordance with Rohani's research [23] which shows that neutrophil values are higher in severe symptoms than in mild symptoms, while the lymphocyte value is lower in severe symptoms compared to mild symptoms and the NLR value is higher in severe symptoms compared to mild symptoms.

SARS-CoV-2 infects cells in the respiratory tract and binds to the ACE2 receptor and makes its way into the cells, then the virus begins to spread through the bloodstream, marked by levels of leukocytes and lymphocytes that begin to decrease [24]. Leukocytes are the most important cellular immune response to fight viruses, while lymphocytes are the main leukocytes that play a role in immunological processes. Lymphocytes play a role in finding and destroying cells infected with viruses and play a role in making antibodies [25]. Neutrophils play a role in the phagocytosis process which attacks and destroys pathogenic microbes [23].

More neutrophils will be produced and accelerate lymphocyte apoptosis when inflammation occurs. Stimulation from viruses and the production of pro-inflammatory cytokines causes neutrophils

to release Neutrophil Extracellular Traps (NETs), which are nucleic acids that are able to trap and kill virus particles [26]. Excessive production of NETs can cause lung damage by NETosis-related enzymes and is associated with the severity of the disease and the extent of lung injury [27]. Neutrophils are also known to produce large amounts of reactive oxygen species (ROS) which can damage cell DNA and remove viruses from cells. Through antibody dependent cell-mediated cytotoxic (ADCC) neutrophils can directly kill viruses [28]. An increase in the number of neutrophils can also be triggered by viral-related inflammatory factors. The increase in neutrophils is an uncontrolled systemic inflammatory response due to the release of large amounts of pro-inflammatory cytokines, causing the typical symptoms of critical COVID-19[23].

The decrease in the number of lymphocytes along with the increase in the severity of symptoms in COVID-19 patients is caused by several potential mechanisms. The first mechanism is that the virus directly infects and kills T lymphocyte cells through the interaction of the ACE2 receptor with the viral S protein [29]. The second mechanism is that the virus infects the lymphatic organs and causes damage to the organs thereby suppressing lymphopoiesis. It should be noted that bone marrow tissue expresses a small number of ACE2 receptors on the haematopoietic cell membrane so that the virus can infect cells causing cell death [30]. The final mechanism is that an excessive increase in the number of pro-inflammatory cytokines causes lymphocyte apoptosis [23].

Over time, patients with mild degrees of severity may experience worsening due to extensive inflammatory processes due to viral infections. NLR is a reflection of the balance between the innate immune response (neutrophils) and adaptive immunity (lymphocytes). As a result of increasing the number of neutrophils and decreasing the number of lymphocytes, the NLR value will increase, so the NLR value can generally be used as a biomarker of systemic inflammatory status so that it can be used as a predictor of the severity of COVID-19 patients[31] [32].

The results of this study show differences in the neutrophil lymphocyte ratio (NLR), neutrophil count and lymphocyte count of COVID-19 patients, where for severe and critical symptoms the NLR value and neutrophil value are higher than for mild and moderate symptoms, whereas for severe and critical symptoms the value lymphocytes are lower compared with mild and moderate symptoms. Examination parameters for COVID-19 patients that can be used besides the neutrophil lymphocyte ratio (NLR) are the monocyte lymphocyte ratio (MLR), Platelet To Lymphocyte Ratio (PLR) and D-dimer. MLR examination parameters can be used to determine the initial response to respiratory infections because monocytes function as the main leukocytes that are attracted to the alveolar in the initial response when an infection occurs [33] PLR and D-dimer parameters can be used to detect severe infections or acute inflammation caused by sepsis, and can also affect blood clotting, such as increasing plasminogen activator inhibitor levels in COVID-19 patients [17].

CONCLUSION

Neutrophilia and lymphocytopenia in COVID-19 patients only occurred in the severe and critical categories so that the average value of high NLR in COVID-19 patients occurred in the severe (6.12%) and critical (10.78%) categories. The NLR value in patients with the severe category had an increase in the NLR value twice the normal value, while in the critical category had an

increase in the NLR value three times the normal value.

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CONFLICT OF INTEREST

Authors declare that there is no conflict of interest in the writing of this academic work.

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