JURNAL RISET KESEHATAN
POLTEKKES DEPKES BANDUNG
Vol 17 No 2, Oktober 2025

e-ISSN: 2579-8103
p-ISSN:1979-8253

CORRELATION OF NEUTROPHIL LYMPHOCYTE RATIO (NLR) VALUES WITH C-REACTIVE PROTEIN (CRP) LEVELS IN PNEUMONIA PATIENTS

Korelasi Nilai Neutrofil Limfosit Ratio (NLR) dengan Kadar C-Reactive Protein (CRP) pada Pasien Pneumonia

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ABSTRAK

Pneumonia merupakan infeksi akut pada paru-paru yang disebabkan oleh mikroorganisme seperti bakteri, virus, atau jamur, yang memicu peradangan dan melemahkan sistem kekebalan tubuh. Deteksi dini penting untuk penentuan strategi pengobatan dan pengurangan risiko komplikasi. Salah satu indikator yang dapat digunakan terhadap respon inflamasi sistemik akibat infeksi pneumonia adalah Neutrofil Limfosit Ratio (NLR). Selain NLR, pemeriksaan kadar C-Reactive Protein (CRP) juga dapat dilakukan untuk mengetahui tingkat aktivitas penyakit infeksi. Tujuan penelitian ini adalah untuk mengetahui korelasi nilai NLR dengan kadar CRP pada pasien pneumonia. Metode penelitian ini adalah deskriptif korelasional dengan pendekatan cross sectional yang dilakukan terhadap 25 pasien pneumonia dewasa dan lanjut usia dengan komorbiditas, yang dipilih melalui pengambilan consecutive sampling. Penelitian ini dilakukan di RS Paru Dr. H. A Rotinsulu dengan waktu penelitian dilakukan pada 06-18 November 2024. Hasil penelitian menunjukkan bahwa nilai rata-rata pemeriksaan neutrofil pada pasien pneumonia adalah 76,9%, limfosit 13,4%, NLR 9,12, dan kadar CRP 83 mg/L. Uji korelasi Spearman menunjukkan korelasi positif yang signifikan antara NLR dan CRP (r=0,415, p=0,039). Hasil ini menunjukkan bahwa nilai NLR yang lebih tinggi berkaitan dengan peningkatan kadar CRP pada pasien pneumonia.

***Kata kunci** : C-Reactive Protein (CRP), Neutrofil Limfosit Ratio (NLR), Pneumonia*

ABSTRACT

Pneumonia is an acute infection of the lungs caused by microorganisms such as bacteria, viruses, or fungi, which trigger inflammation and weaken the immune system. Early detection is crucial for guiding treatment strategies and reducing the risk of complications. One indicator that can be used for the systemic inflammatory response due to pneumonia infection is the Neutrophil Lymphocyte Ratio (NLR). In addition to NLR, C-Reactive Protein (CRP) levels can also be examined to determine the level of infectious disease activity. This study aimed to assess the correlation between NLR values and CRP levels in pneumonia patients. This is a descriptive correlational study with a cross-sectional design that was conducted on 25 adult and elderly pneumonia patients with comorbidities, selected through consecutive sampling. This research was conducted at Dr. H. A. Rotinsulu Lung Hospital, with the research time being November 6 –18, 2024. The mean neutrophil percentage was 76.9%, lymphocytes 13.4%, NLR 9.12, and CRP level 83 mg/L. Spearman's correlation test showed a significant positive correlation between NLR and CRP (r=0.415, p=0.039). These results indicate that higher NLR values are associated with increased CRP levels in pneumonia patients.

Keywords: C-Reactive Protein (CRP), Neutrophil Lymphocyte Ratio (NLR), Pneumonia

https://doi.org/10.34011/juriskesbdg.v17i2.2831

e-ISSN: 2579-8103
p-ISSN:1979-8253

INTRODUCTION

Pneumonia is an acute infectious disease of the lung tissue that can be caused by various microorganisms, including bacteria, viruses, and fungi.[1] Pneumonia infection occurs when pathogens such as bacteria, lower the body's immune system and trigger inflammation in the lung tissue.[2] Pneumonia remains a leading cause of morbidity and mortality worldwide. The most common signs and symptoms of pneumonia in adults are shortness of breath, cough, and fever.[3]

According to epidemiological data, in 2015, there were approximately 56.4 million cases of pneumonia recorded, with the number of deaths reaching 3.2 million people.[4] In Europe, the incidence of pneumonia ranges from 1.07 to 1.2 cases per 1,000 population annually, significantly lower than in Asia, which records up to 16.9 cases per 1,000 population per year. According to the 2023 National Basic Health Research Report (Riskesdas), pneumonia cases in Indonesia reached 877,531 across all age groups. West Java Province ranked first, contributing 156,977 cases (17.88%).[5]

Early detection and assessment of pneumonia severity are crucial for determining appropriate treatment strategies and reducing the risk of complications. Laboratory tests are necessary to support a pneumonia diagnosis. According to a 2019 study by Wasita et al., one indicator that can be used to assess the systemic inflammatory response due to pneumonia infection is the Neutrophil Lymphocyte Ratio (NLR).[6]

The neutrophil-lymphocyte ratio (NLR) is a relatively cost-effective and easier-to-calculate parameter, requiring only a complete blood count.[7] In pneumonia, the NLR can increase. Lymphocytopenia and neutrophilia are physiological reactions of the innate immune system to systemic inflammatory phenomena, especially when caused by bacterial infections, such as pneumonia.[8] From the results. Previous research found that the NLR test had a specificity of 89.8% and a sensitivity of 88.8% in diagnosing Community Acquired Pneumonia (CAP) patients. This percentage is the highest compared to other peripheral blood leukocyte markers.[9]

In addition to NLR, C-Reactive Protein (CRP) level examination can also be performed to determine the level of infectious disease activity.[10] CRP is an acute-phase protein produced by the liver as a non-specific immune response to infection.[11] When there is a viral infection, bacteria, non-infectious inflammation, or malignancy, CRP levels can increase, including in patients with pneumonia. However, the concentration of CRP levels increases depending on the cause.[12] Within 10-12 hours after infection, CRP levels will increase significantly.[13] In patients with severe pneumonia, there is a high increase in CRP levels.[14]

A 2020 study by Chen et al. found that higher plasma CRP levels indicated severe COVID-19 pneumonia and longer hospitalization duration. A 2020 study by Mousavi-Nasab et al. showed a positive correlation between NLR and CRP levels in COVID-19 patients. However, the correlation between NLR and CRP in pneumonia patients in general has not been extensively studied. Previous research by Fristiani et al. (2022) found a significant association between NLR and CRP levels and disease severity in COVID-19 patients.[15]

This study aims to determine the correlation between Neutrophil Lymphocyte Ratio (NLR) values and C-Reactive Protein (CRP) levels in pneumonia patients.

METHODS

This study used a descriptive correlational design with a cross-sectional approach to assess the correlation between NLR values and CRP levels in pneumonia patients. This study was conducted at Dr. HA Rotinsulu

https://doi.org/10.34011/juriskesbdg.v17i2.2831

e-ISSN: 2579-8103
p-ISSN:1979-8253

Lung Hospital, located at Jl. Bukit Jarian No. 40, Bandung. The study was conducted from November 6–18, 2024.

This research has received ethical approval from the Health Research Ethics Commission (KEPK) of Dr. HA Rotinsulu Lung Hospital No. LB 01.02/12777/2024.

Population and Sample

The population of this study was all patients diagnosed with pneumonia who were hospitalized at Dr. HA Rotinsulu Lung Hospital in November 2024. The sample used in this study was 25 pneumonia patients who had given informed consent as research samples taken by consecutive sampling, where the selection of research samples was by determining subjects who met the criteria within a certain period. The inclusion criteria were adult patients (19-59 years) and elderly patients (≥60 years) with a diagnosis of pneumonia, both with and without comorbidities, who had undergone a complete hematology examination. The exclusion criteria were blood samples that experienced hemolysis.

Data Collection Method

The data used is primary data. The Neutrophil Lymphocyte Ratio (NLR) value was taken from the results of a complete hematology examination of pneumonia patients using a Sysmex XN-450 device, then calculated using the formula total neutrophil count divided by total lymphocyte count. C-Reactive Protein (CRP) levels were measured using an Afinion 2 Analyzer from blood samples from pneumonia patients. The blood samples used were leftover samples from laboratory tests on the same day. Patient characteristics such as gender, age, comorbidity status, and disease severity were obtained from medical records. The normal CRP value is <5 mg/L, while the NLR value, as a marker of inflammation, is >3.13.

Data analysis

Data analysis techniques, descriptive univariate analysis was used to determine the frequency distribution of patient characteristics such as gender, age, comorbidity status, severity, and bacteriological examination. Furthermore, the minimum, maximum, and average values of each variable, namely the NLR and CRP levels, were determined in pneumonia patients. Furthermore, a non-parametric Spearman statistical test was performed to determine the correlation between NLR and CRP values in pneumonia patients.

RESULTS

This study was conducted at Dr. HA Rotinsulu Lung Hospital located at Jl. Bukit Jarian No. 40 Bandung on November 6-18, 2024. The subjects of the study were all patients with a diagnosis of pneumonia who were hospitalized at Dr. HA Rotinsulu Lung Hospital who met the inclusion criteria, totaling 25 patients. The details of the characteristics of pneumonia patients are shown in Table 1 as follows:

Table 1. Characteristics of Pneumonia Patients

Characteristics	Frequency (n)	Percentage (%)
Gender		
Male	20	80
Female	5	20
Age		
Adult (19–59 years)	13	52
Elderly (≥60 years)	12	48
Comorbidities		
COPD	14	56
Lung Tumor	1	4

https://doi.org/10.34011/juriskesbdg.v17i2.2831

e-ISSN: 2579-8103
p-ISSN:1979-8253

Characteristics	Frequency (n)	Percentage (%)
Pulmonary TB	5	20
Diabetes Mellitus	4	16
Miliary TB	1	4
Lung Cancer	3	12
Asthma	2	8
Severity		
Mild	0	0
Moderate	22	88
Severe	3	12
Bacteriological Examination		
Gram Staining		
Gram-positive cocci & Gram-negative bacilli	10	40
Gram-positive cocci	1	4
Gram-negative bacilli	3	12
Not examined	11	44
Culture		
Positive	3	12
Negative	1	4
Not examined	21	84
No bacteriological test performed	11	44

Based on Table 1, the study was conducted by collecting data from medical records. Researchers analyzed 25 patients, the majority of whom were male (80%) and in the adult (52%) and elderly (48%) age groups. Most pneumonia patients had the most comorbid disease, namely Chronic Obstructive Pulmonary Disease (COPD) (56%). The severity of pneumonia was predominantly in the moderate category (88%). Bacteriological examination using Gram staining showed that 40% of samples contained Gram-positive Cocci and Gram-negative rods (12%), while 44% were not examined. In culture examination, only 12% showed positive results, 4% were negative, and 84% were not examined.

Table 2. Descriptive Univariate Test

Mark	N (%)	Min	Max	Mean
Neutrophils (%)	25	52	92.4	76.9
Lymphocytes	25	2.7	31.5	13.4
(%)	25	1.82	34.22	9.12
NLR	25	5	159	83
CRP (mg/L)				

Based on Table 2, the results of the descriptive univariate test on 25 samples of pneumonia patients showed that the average neutrophil value was 76.9% with a minimum value range of 52% and a maximum of 92.4%. The lymphocyte value had an average of 13.4% with a minimum value of 2.7% and a maximum of 31.5%. The NLR value showed an average of 9.12 with a minimum value of 1.82 and a maximum of 34.22. Meanwhile, the CRP level had an average of 83 mg/L with a minimum value range of 5 mg/L and a maximum of 159 mg/L.

https://doi.org/10.34011/juriskesbdg.v17i2.2831

e-ISSN: 2579-8103
p-ISSN:1979-8253

Table 3. Spearman Correlation Test

Variables	Correlation Coefficient (r)	Significance (p)
NLR with CRP	0.415	0.039

Based on Table 3, the Spearman correlation test between NLR and CRP levels yielded a significance value (p=0.039) lower than 0.05, indicating a significant positive correlation between the NLR and CRP variables. This means that as NLR increases, CRP levels tend to increase as well. However, the strength of this relationship is considered moderate, with a correlation coefficient of r=0.415.

DISCUSSION

This study shows that 80% of pneumonia patients are men compared to 20% of women. This is in line with previous research which stated that the proportion of pneumonia cases in men was 53.95% and 46.05% in women.[16] This is caused by the risk factor of smoking.[17] However, in this study it was not known whether the patients had a smoking habit or not. Gender differences play an important epidemiological factor in a number of diseases, including respiratory tract disorders. Women tend to be more susceptible to upper respiratory tract infections, while men more often experience infections in the lower respiratory tract. Overall, respiratory tract diseases, especially community-acquired pneumonia, are more common in men. This may be associated with differences in body anatomy, lifestyle habits, behavioral patterns, and socioeconomic factors between men and women.[18] Meanwhile, the number of adult and elderly pneumonia patients was almost equal in this study.

The results of descriptive analysis showed a significant increase in the inflammatory values of NLR and CRP in pneumonia patients with comorbidities. The average neutrophil level of patients was 76.9%, with a range of 52-92.4%. The highest levels were found in patients with pulmonary Ca, and the lowest in patients with asthma. The average lymphocyte was 13.4% with a range of 2.7-31.5%, the highest in COPD patients and the lowest in pulmonary Ca. The average NLR value was 9.12 with a range of 1.82-34.22. The highest levels were found in pulmonary Ca and the lowest in COPD. Meanwhile, the average CRP level was 83 mg/L, with a range of 5-159 mg/L, the highest values were found in patients with pulmonary TB and pulmonary Ca, and the lowest in asthma. The average NLR and CRP values that were higher than the normal threshold indicated an acute inflammatory response in pneumonia patients. The normal value of CRP <5 mg/L while the NLR value as a marker of inflammation according to PDS PatKlin is >3.13. An elevated NLR indicates neutrophil dominance due to infection, while CRP is an inflammatory biomarker produced by the liver in response to bacterial infection. In this study, pneumonia patients experienced serious lung infection and inflammation, generally caused by viruses, bacteria, or fungi.

The host inflammatory response plays a crucial role in the development and progression of pneumonia, particularly in older adults. Neutrophilia and lymphocytopenia are physiological responses of the innate immune system to systemic inflammation. Lymphocytopenia consists of accelerated apoptosis and margination of lymphocytes in the reticuloendothelial system, liver, and splanchnic lymphatic system, and redistribution of lymphocytes within the lymphatic system. Neutrophilia is the opposite phenomenon during systemic inflammation, resulting from neutrophil demargination and stem cell stimulation by growth factors (granulocyte colony-stimulating factor).[19]

The Neutrophil-Lymphocyte Ratio (NLR) consists of two important

https://doi.org/10.34011/juriskesbdg.v17i2.2831

e-ISSN: 2579-8103
p-ISSN:1979-8253

components in inflammation: neutrophils and lymphocytes. High NLR levels can indicate the number of neutrophils in the blood, which is a follow-up response to Interleukin (IL-8) produced by innate immune cells. Interleukin (IL-8) is a cytokine and chemokine produced along with other innate pro-inflammatory cytokines such as IL-1, IL-2, IL-6, IL-12, and TNF-alpha. Neutrophils have a direct relationship with IL-8, as well as with IL-6. In addition, hepatocytes produce CRP in response to IL-6, which is captured by hepatocyte receptors. Theoretically, this indicates that CRP values should be in line with the NLR.[20]

C-Reactive Protein is used to determine the severity and prognosis of pneumonia. Higher CRP levels indicate a more severe infection. The effects of CRP produced by the liver may differ from those produced by bacterial infections. Theory suggests that viral infections result in low CRP levels, while bacterial infections generally increase CRP levels.[20,21] His occurs because bacterial infections trigger more extensive inflammation, which then increases the release of the cytokine Interleukin-6, one of the cytokines that stimulates CRP production.[22]

The immunological response pathways to bacteria and viruses differ. Macrophages respond first by phagocytosis and produce pro-inflammatory cytokines in response to bacterial infection. Among these pro-inflammatory cytokines, IL-6 is captured by receptors on hepatocytes, followed by CRP production by the liver. The process differs in viral infections. Interferon (IFN) is the dominant pro-inflammatory cytokine produced in response to viral infection. This interferon-dominated immunological response may be the underlying cause of low CRP production by hepatocytes, despite continued production as an inflammatory response.[20]

Several factors that increase the risk of pneumonia include advanced age over 60 years, the presence of comorbidities such as diabetes mellitus, chronic obstructive pulmonary disease (COPD), cardiovascular disorders, malignancies, kidney failure, chronic liver disease, and neurological disorders. Other contributing factors include excessive alcohol consumption, malnutrition, smoking, immunosuppression, and infections caused by Gram-negative bacteria.[23]

In this study, the most common comorbidity was COPD, accounting for 56%. This finding aligns with previous research by Chen et al. in 2021. COPD also significantly influences the severity and course of pneumonia, with COPD patients with pneumonia tending to have significantly higher blood CRP levels.[24]

The second most common comorbidity is pulmonary TB, accounting for 20%. According to a 2019 study by Kan et al., 20.9% of TB patients are at risk of co-infection with other bacteria, making them more susceptible to pneumonia. Furthermore, the presence of TB can also worsen a patient's prognosis.[25]

Previous research has shown that individuals with diabetes mellitus (DM) have a higher risk of developing community-acquired pneumonia (CAP) and poorer treatment outcomes. Compared with CAP patients without diabetes, diabetic patients tend to be older, have more comorbidities, and have an increased risk of pleural effusion and mortality.[26] A 2019 study by Ferreira et al. also revealed that patients with type 2 diabetes (22.7%) had a higher rate of hospitalization and an increased risk of morbidity and mortality.[27]

Other comorbidities identified in this study included lung cancer (12%), asthma (8%), lung tumors (4%), and miliary tuberculosis (4%). Lung cancer and tumors are known risk factors for pneumonia, particularly in elderly patients. This condition is thought to be caused by decreased immunity due to the use of hormones,

https://doi.org/10.34011/juriskesbdg.v17i2.2831

e-ISSN: 2579-8103
p-ISSN:1979-8253

immunosuppressants, or chemotherapy.[28]

Sputum culture results in this study indicated pneumonia infection caused by the Gram-negative bacteria Pseudomonas aeruginosa and Acinetobacter Iwoffii. Acinetobacter Iwoffii is a Gram-negative, aerobic, non-fermentative bacterium seen as a normal flora of the oropharynx and skin in approximately 25% of healthy individuals. Due to its ubiquitous nature, this bacterium is classified as an opportunistic pathogen that tends to infect individuals with impaired immune systems, and is known to cause various nosocomial infections such as septicemia, pneumonia, meningitis, urinary tract infections, and skin and wound infections.[29] Of the 25 patients diagnosed with pneumonia in this study, not all underwent bacteriological examination. This examination was performed at the request of the DPJP doctor, which is usually adjusted to the patient's clinical condition. Therefore, the cause of pneumonia cannot always be determined in all patients.

The correlation test conducted in this study showed a significant positive correlation (p=0.039) between the NLR and CRP variables. This means that as the NLR value increases, the CRP value tends to increase as well. However, the strength of this relationship is considered moderate, with a correlation coefficient of r=0.415. Nevertheless, it can be said that each pneumonia patient with comorbidities has varying NLR and CRP values. This is influenced by variations in the body's inflammatory response, the severity of the infection, the immune system, and the type of comorbidities each patient has.

A limitation of this study is that comorbidities and other conditions that can increase CRP levels in pneumonia patients cannot be completely ruled out, as the majority of pneumonia patients have comorbidities. Furthermore, this study used a consecutive sampling technique, which selects subjects who meet criteria within a specific time period. Further research is needed to determine the correlation between NLR and CRP levels in pneumonia patients without comorbidities. This research should involve a longer study period and a larger sample size.

CONCLUSION

The results of the study showed that there was a significant correlation with sufficient strength of relationship between the Neutrophil Lymphocyte Ratio (NLR) and C-Reactive Protein (CRP) levels in pneumonia patients, and the direction of the positive relationship indicated that an increase in NLR was related to an increase in CRP levels in pneumonia patients.

The average neutrophil count in pneumonia patients was 76.9% (range 52-92.4%), lymphocyte count 13.4% (2.7-31.5%), and NLR 9.12 (1.82-34.22). Meanwhile, the average CRP level was 83 mg/L with a range of 5-159 mg/L.

It is recommended that future researchers use a larger sample size to ensure the results are more valid and more representative of the broader population. Researchers should also consider sample inclusion criteria, including pneumonia patients without comorbidities, to reduce potential bias that could influence the correlation analysis results. Researchers are advised to consider more specific inclusion criteria for comorbidities (e.g., pneumonia with comorbid COPD).

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