

Association of the Neutrophil-Lymphocyte Ratio with Lung Function in Patients with Chronic Obstructive Pulmonary Disease at RSUD Sanjiwani Gianyar 2022

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Abstract: Background: Chronic Obstructive Pulmonary Disease is characterized by persistent airway obstruction accompanied by a chronic inflammatory response. Neutrophil-lymphocyte ratio widely used to explain inflammatory processes in many diseases. This study aims to evaluate the association between NLR and lung function. Methods: This study is a cross-sectional study with 42 samples of COPD patients who visited the pulmonary department of Sanjiwani hospital between February 2022 - May 2022. The value of NLR is calculated based on the ratio of the absolute value of neutrophils and lymphocytes from the results of routine blood tests. Lung Function test by measuring forced expiratory volume in 1 second (FEV1), Forced vital capacity (FVC), and FEV1/FVC with spirometry. All the data is analyzed with Spearman's Correlation test and Independent T-Test. Results: Based on a total of 42 patients, most are male (57.1%) and 42.9% female. The highest age range at 60-69 years and >70 years, 40.5% in each group. Spearman correlation showed a positive correlation between NLR and COPD group ($r = 0.369$, $p = 0.016$). The Independent T-test showed a significant difference in lung function in patients with low NLR (<3.00) and high NLR (3.00) with a difference in FEV1 0.6043 mL ($p = 0.000$). Conclusions: NLR can be used as a simple hematological marker in determining the inflammatory process in the course of COPD patients.

Keywords: Neutrophil-lymphocyte ratio, Chronic Obstructive Pulmonary Disease, Lung Function, Forced expiratory volume in 1 second (FEV1), Forced vital capacity (FVC), and FEV1/FVC

1. Introduction

Chronic obstructive pulmonary disease is characterized by persistent airway obstruction and a chronic inflammatory response.¹The diagnosis and severity of COPD describe the intensity of inflammation in the small airways (mucosal edema, fibrotic remodeling of the airways, and mucus impaction) and allow the increased cholinergic activity in the airway muscles.²Decreased capability and enhancement airway resistance result in decreased airflow, specifically during expiration which prolongs the expulsion of air from the lungs. This form the spirometry results by looking at the forced expiratory volume after one second (FEV1) and forced vital capacity (FVC), less than 0.7 (FEV1/FVC < 0.7).¹Enhancement and activation of macrophages and neutrophils plays an important role in chronic inflammatory COPD. Increase number of neutrophils and macrophages found in the sputum samples caused by the accumulation of neutrophils and monocytes from the circulation it is a response to chemotactic mediators from airway epithelial cells and macrophages in the lung.^{3,4}Furthermore, there was an increase in lymphocytes in the lungs, including CD8 cells that indicated an increase in bacterial Toll-like receptors (TLR) and the presence of bacterial colonization.⁵This suggests a role for lymphocytes and neutrophils in COPD inflammation and may explain the persistence of inflammation, even when patients quit smoking.⁶

Several studies clarify and prove the relationship between simple changes in hematological parameters and degradation of lung function. NLR can be a new prognostic marker that can interpret lung function in COPD patients. Therefore, this marker can be an effective, simple, and relatively

inexpensive tool in determining the lung function of COPD patients.

The study that discusses the association between hematological indications and pulmonary function of patients with COPD is still infrequently. This study focuses on simple hematological hypotheses, such as NLR that may be associated with pulmonary function in COPD patients. Therefore, the object of this study was to examine the relationship between NLR and lung function.

2. Methods

This study is a cross-sectional study with primary data collection, specifically routine blood tests in patients with Chronic Obstructive Pulmonary Disease at the Sanjiwani Hospital, Gianyar, from February 2022 - May 2022. Sampling by consecutive sampling with a total of 42 patients that comply with the inclusion criteria. This research conforms to the research permit with Ethical Clearance No. 60/PEPK/XIII/2022 from the research ethics committee of the Sanjiwani Hospital, Gianyar.

The samples were all COPD patients diagnosed by a pulmonologist who completed the inclusion criteria. The diagnosis of COPD is based on anamnesis, physical examination, and supporting investigation (Spirometry and routine blood test) at the Pulmonary Department of Sanjiwani Hospital, Gianyar. Meanwhile, COPD patients with signs of infection/abnormal WBC values (normal range 4000-12000 cells/mL), autoimmune disease, malignancy, or bleeding were exclusion criteria in this study.

The participants signed an informed consent agreement to be a sample. Data retrieval of gender, age, BMI, smoking history, and evaluation of clinical symptoms. The COPD assessment test (CAT) used to evaluate the clinical symptoms of the sample, consisting of 8 questions, each with a score of 0-5 based on severity and calculation of these assessments used to assess the severity of the disease. NLR ratio was calculated as the absolute count of neutrophil divided by total count of lymphocytes, and measured with Mindray Hematology Analyzer BC 5150. This study classifies the NLR into low and high with a cut-off point of 3.00.⁷ Information about FEV1, FVC, and FEV1/FVC using SMP 21/01 RD Spirometer. In this study, FEV1 is used as a reference in lung function by measuring differences in FEV1 values based on age and height compare to normal values of Indonesian lung function.⁸ Smoking history was obtained through history taking and measuring the degree of mild, moderate, and severe using the Brinkman Index.⁹ COPD diagnoses divided into COPD groups based on GOLD 2021, namely groups A, B, C, and D (FEV1/FVC <70%, FEV1 <80%).¹

In this study, the analyzed data using the 26th version of SPSS. Statistical analysis methods were descriptive statistical calculations, Spearman Correlation Test, and Independent t-test. The test results are significant if the value of p is <0.05.

3. Results

Sample Characteristics

Based on all the participants, obtained most are male (57.1%), with the highest age range at 60-69 years and >70 years, 40.5% in each group. Body Mass Index (BMI) is considerable in the group underweight (71.4%), and the distribution of each smoking status is not smoking (28.6%), mild (7.1%), moderate (45.9%), and severe (19.0%). The distribution of the majority of COPD groups in group B (52.4%). (Table 1)

Correlation between NLR with age, BMI, smoking history, and COPD group

Spearman's test found that NLR has low correlation ($r=0.369$) to COPD group with high significance ($p=0.016$). This result showed that the NLR and COPD groups had a positive correlation. However, no significant association between NLR with age, BMI, and smoking history in this study. (Table 2)

Distribution of NLR to Lung function

Independent T-test between NLR and lung function has a value of $p=0.000$ ($p<0.05$). The high NLR (≥ 3.00) and low

(<3.00) have a significant decrease in lung function. This study showed a decrease of FEV1 in COPD patients with low NLR in the amount of 0.6994 mL, its way lower compared to high NLR, which has a decrease of FEV1 in 1.3037 mL. Resumed that NLR has an important role in the change of lung function. (Table 3) (Graph 1)

Table 1: Characteristic Samples

Variable	Category	n (%)
Sex	Male	24 (57.1)
	Female	18 (42.9)
Age	<50	2 (4.8)
	50-59	6 (14.3)
	60-69	17 (40.5)
	>70	17 (40.5)
Smoking History	No history of smoking	12 (28.6)
	Mild	3 (7.1)
	Moderate	19 (45.2)
	Severe	8 (19.0)
BMI	Underweight	30 (71.4)
	Normal	10 (23.8)
	Overweight	2 (4.8)
COPD group	A	5 (11.9)
	B	22 (52.4)
	C	1 (2.4)
	D	14 (33.3)

Table 2: Correlation between NLR with age, BMI, smoking history and COPD group

Variable	NLR	
	r	p
Age	0.094	0.554
BMI	-0.179	0.256
Smoking history	0.251	0.109
COPD group	0.369	0.016

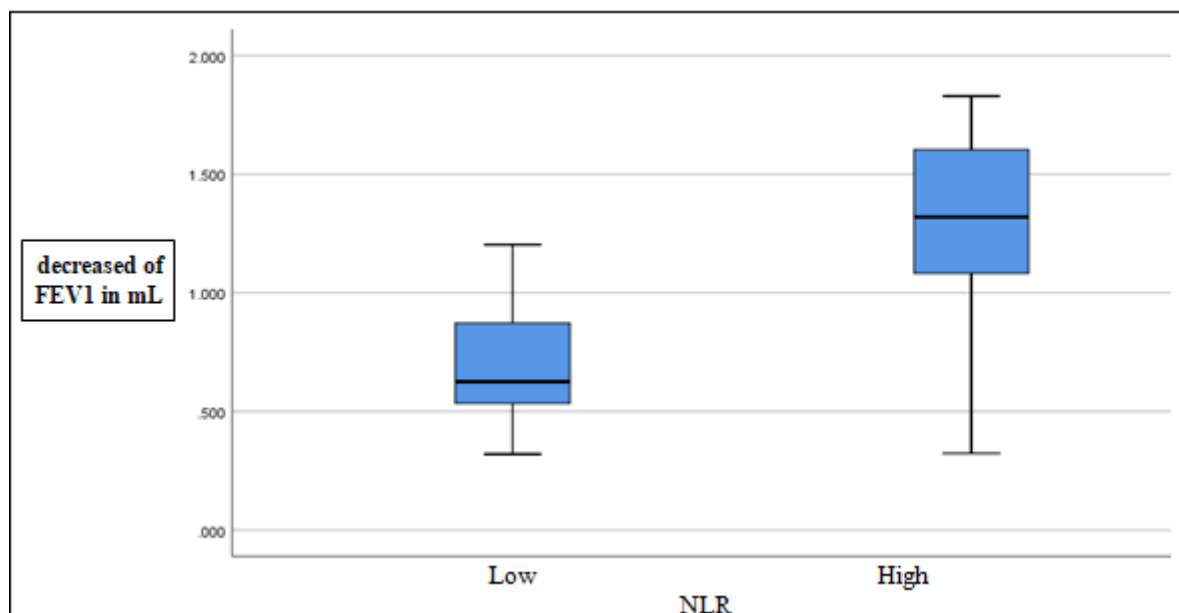
** Spearman's Correlation, has significant value if $p < 0.005$. Correlation Coefficient in Spearman's (very low correlation $r=0.00-0.199$, low correlation $r=0.20-0.39$, moderate correlation $r=0.40-0.599$, strong correlation $r=0.60-0.799$, very strong correlation $r=0.80-1$).

A positive coefficient correlation means that two variables have a reciprocal association, and a negative correlation means that two variables have the opposite.

Table 3: The distribution between NLR and Decreased lung function (FEV1 in mL)

NLR	Mean \pm SD	Mean difference	N	Sig.
Low	0.6994 \pm 0.249	-0.6043	21	0.000
High	1.3037 \pm 0.384		21	

** Independent T Test, significant if value of $p < 0.05$



Graph 1: The distribution between NLR and Decreased lung function (FEV1 in mL)

4. Discussion

A total of 42 samples of COPD patients who were eligible completed the study. Based on all the participants, obtained most are male (57.1%), with the highest age range at 60-69 years and >70 years, 40.5% in each group. This result supported by a previous study by Wei et al, which examined the prognosis of COPD with routine blood tests with a sample of 368 patients, the majority of the participants were male (68.5%) then the highest age range at 70.6 years.¹⁰ Similar results also found by In et al study that examined the importance of NLR on lung function in COPD patients who males (80.9%) as the majority of the sample.¹¹ These results differ from the risk factors for COPD that more common in women than men.¹

Focuss of this study is to evaluate the association between *Neutrophil-lymphocyte ratio* (NLR) to lung function. NLR was a simple hematologic finding that represent an inflammatory process and risk of exacerbation in COPD patients. Independent t-test, found that patients with high NLR (≥ 3.00) had worse lung function (FEV1 - 1.3037 mL) than those with low NLR (< 3.00) (FEV1 - 0.6994 mL) with significant results. ($p = 0.000$). The same results were found in Xu Gao et al who stated that NLR was significantly ($p < 0.001$) associated with decreased lung function parameters. NLR significantly reduced the mean FEV1 0.021 (0.004) L, FVC 0.016 (0.005) L, FEV1/FVC 0.290% (0.065%), and MMEF 3,865 (0.916) L/min.¹² Similar results were also obtained from the study of Sakurai et al comparing the mean FEV1 (%) in patients with NLR < 2.7 (FEV1 $66.5 \pm 20.4\%$) and 2.7 (FEV1 $55.8 \pm 21.3\%$) ($p = 0.0003$).¹³ In Lee et al study found a significant relationship ($p = 0.001$) between NLR to FEV1% and performed that NLR with the highest quartile could be an independent predictor of COPD exacerbation in the first year of follow-up.¹⁴ Another study found that NLR was significantly associated with FEV1 ($r=0.367$, $p < 0.001$).¹⁵

As an inflammatory marker, NLR was a simple hematologic finding to detect inflammatory processes in COPD patients.

Information of NLR potentially represent airway obstruction or exacerbation in COPD, and correlated to the quality of life and progress of the disease.^{14,15} Underlying mechanism between NLR and airway obstruction/ exacerbation is still unclear. Several studies showed that neutrophil was a primary mediator in the decrease of lung function in COPD. When activated, neutrophils release several proteolytic enzymes, such as elastase and matrix metalloproteinases, who contribute the develop of emphysema.¹⁶ And previous studies have shown that NLR is an independent predictor of future exacerbations.^{14,15} Therefore, NLR was an inexpensive and accessible test used to predict the exacerbations in various health services.^{11,14,15} Based on the results of this analysis, NLR is one of the markers in showing the presence of an inflammation that plays an essential role in the exacerbation of COPD patients.

The correlation between NLR and other variables. GOLD group/classification and NLR showed a positive correlation in this study. The higher NLR value significantly correlated with higher GOLD classification ($p=0.016$) in a weak correlation ($r = 0.369$). This positive correlation is consistent with Billir et al, who found a linear increase between NLR and the stable COPD group. In that study, NLR has no significant increase in group A, but there was a big difference in the NLR value of group D compared to groups B and C ($p = 0.001$).¹⁷ Different result from Duyar et al, that shown no significant relationship between NLR values and smoking history, cardiovascular comorbidities, exacerbation rate, airway obstruction, and GOLD classification.¹⁸ While the correlation test between NLR with age, BMI, and smoking status did not show a significant relationship in this study.

5. Conclusion

This study showed a significant relationship between NLR and lung function. And there is a significant relationship between NLR and GOLD classification with a weak correlation stage. This simple hematological examination is able to provide a quick, inexpensive and accessible

description of the occurrence of chronic inflammation that affects lung function

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