Journal of
Cardio - Thoracic Medicine

http://jctm.mums.ac.ir

The Role of Neutrophil to Lymphocyte Ratio in Predicting Clinical Outcomes in Chronic Obstructive Pulmonary Disease Patients: A Single-Center Cohort Study

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ARTICLE INFO

Article type:
Original Article

Article history:
Received: 28 July 2024
Revised: 4 December 2024
Accepted: 10 December2024

Keywords:
Chronic Obstructive Pulmonary Disease
Neutrophil-Lymphocyte Ratio
Biomarkers

ABSTRACT

Introduction: The primary objective of the study was to scrutinize the neutrophil to lymphocyte ratio (NLR) in patients afflicted with chronic obstructive pulmonary disease (COPD).

Methods: This study, conducted at Mashhad University of Medical Sciences in Iran between 2021-2022, aimed to analyze the NLR. Data were collected from medical records, laboratory reports, and personal interviews, focusing on demographic data, clinical histories, and various laboratory and clinical parameters. The severity of COPD was assessed using several clinical scales and spirometry measurements. Statistical analysis was performed using SPSS and R software.

Results: In this study, a cohort of 49 patients with COPD was analyzed, with a majority being male (59%) and having an average age of 62.3 years. The mean NLR was 2.1. The correlation analysis showed a moderate negative correlation between Ejection Fraction and NLR (rho = -0.30, p = 0.03), and a weak positive correlation between Erythrocyte Sedimentation Rate and NLR (rho = 0.28, p = 0.04). Comparative analysis of NLR with COPD clinical scales showed a significant rise in NLR from category 0 to 2 in AECOPD cases (p=0.04). Concurrent ROC analysis indicates a diagnostic power of 0.68, establishing an NLR cutoff value of 1.67, with a sensitivity of 0.67 and a specificity of 0.71.

Conclusions: NLR may serve as a marker for mild to moderate exacerbations in COPD patients (categories 1 and 2); however, its predictive value for severe exacerbations (category 3) remains unclear. Further research is needed to explore the underlying mechanisms and its utility across the full spectrum of exacerbation severity.

► *Ebrahimzadeh, F., Mozdourian, M., Khatami, S., Gandomi Sani, F., Azmon, M., Moodi Ghalibaf, A.A., Abedinzadeh, A. The Role of Neutrophil to Lymphocyte Ratio in Predicting Clinical Outcomes in Chronic Obstructive Pulmonary Disease Patients: A Single-Center Cohort Study. J Cardiothorac Med. 2024; 12(3): 1402-1409. Doi : 10.22038/jctm.2024.81485.1465*

Introduction

Chronic obstructive pulmonary disease (COPD) stands as a prominent respiratory condition, marked by ongoing breathing difficulties and restricted airflow, often escalating to increased inflammation in the lungs and airways. The prevalence of COPD is notably high, especially in low- to middle-

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income nations where individuals are more exposed to risk factors. The limited access to affordable healthcare and diagnostic facilities in these areas accentuates the need for developing dependable and economically viable indicators for monitoring COPD's progression and intensity.(1)

As we delve further into the research surrounding COPD, it is clear that numerous factors have been pinpointed as potential indicators of the disease's advancement. Key measurements such as FEV1 and the FEV1/FVC ratio are central to evaluating the potential progression of COPD. Additionally, aspects like the patient's age, history of smoking, and increased levels of C-reactive protein are vital elements to consider in a thorough assessment of COPD progression (2).

In light of this, the neutrophil-to-lymphocyte ratio (NLR) has surfaced as a promising biomarker, providing a window into the immune reactions to various pathogens and non-infectious agents. Its application is not confined to respiratory illnesses, as it has proven to be a trustworthy marker in identifying ongoing inflammation related to cancer and as a prognostic tool for solid tumors (3-6). The multifaceted nature of NLR as a biomarker opens up new avenues for exploration, potentially leading to more refined strategies in managing COPD.

With this substantial foundation, our research seeks to closely examine the role of the neutrophil-to-lymphocyte ratio (NLR) in individuals grappling with COPD. We posit that fluctuations in the NLR might act as a crucial sign of COPD development, offering a fresh lens through which to comprehend the intricate pathology of the disease. Through rigorous analysis, we aim to determine the reliability of NLR as a marker in gauging COPD severity, thus aiding in the wider initiatives to improve COPD management and therapeutic approaches.

To achieve this goal, we envision a thorough investigation that includes an in-depth review of existing data, complemented by innovative research pathways. By exploring the complex relationship between NLR and COPD, we hope to cultivate a deeper insight that could potentially transform the approach to COPD care, navigating towards a future where individualized medicine becomes a tangible and achievable reality.

Materials and Methods

Study Design and Participants

This prospective cohort study was conducted in the Mashhad, Iran, specifically targeting patients visiting the outpatient respiratory clinic at the Mashhad University of Medical Sciences between the years 2021-2022. The primary objective of the study was to scrutinize the neutrophil to lymphocyte ratio (NLR) in patients afflicted with COPD.

The participant pool was carefully selected based on stringent inclusion and exclusion criteria. Individuals aged between 40 and 80 years who willingly filled out the informed consent were considered eligible for the study.

The study included patients with stable chronic obstructive pulmonary disease (COPD) who were not experiencing an acute exacerbation at the time of enrollment. Patients were excluded if they were in the acute exacerbation phase of COPD, characterized by a sudden worsening of respiratory symptoms requiring additional treatment such as systemic corticosteroids, antibiotics, or hospitalization. This ensured that the study focused exclusively on the evaluation of NLR and other parameters in stable COPD conditions, minimizing confounding factors associated with exacerbation-related inflammatory changes.

A total of 49 COPD patients were meticulously chosen to be part of this research endeavor.

Data Collection and assessments

Data collection was meticulously conducted through a detailed review of patients' medical records and laboratory reports, complemented by personal interviews. The demographic data harvested encompassed age, gender, occupation, and lifestyle habits such as smoking and substance use. Clinical histories were documented, highlighting the presence of ischemic heart disease (IHD), hypertension (HTN), and diabetes mellitus (DM).

Laboratory records were scrutinized to evaluate the neutrophil to lymphocyte ratio

(NLR) and a complete blood count which included parameters such as red blood cell (RBC) count, hemoglobin (Hb) concentration, and platelet (PLT) count. In addition, the white blood cell (WBC) differential count and biochemical tests, including fasting blood sugar (FBS) and ferritin levels, were analyzed.

Clinical parameters were assessed both from the medical records and through interviews. These parameters included systolic and diastolic blood pressure (SBP and DBP), and oxygen saturation (SpO2). The severity of COPD was gauged using various clinical assessment scales such as the Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) categories, the modified Medical Research Council (mMRC) Dyspnea Scale, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Spirometry Classification, and the GOLD Combined Assessment scales. The COPD Assessment Test (CAT) was also utilized, derived from interviews, to gauge the impact of COPD on the patients' health status.

Patients with acute exacerbations of COPD (AECOPD) were classified into three categories based on the severity of their symptoms and the required level of medical intervention. The classification criteria were as follows:

- **Category1** (Mild Exacerbation): Managed with increased doses of bronchodilators and did not require systemic corticosteroids or antibiotics.
- **Category 2** (Moderate Exacerbation): Required systemic corticosteroids and/or antibiotics but did not necessitate hospitalization.
- **Category 3** (Severe Exacerbation): Required hospitalization due to severe respiratory distress, significant hypoxemia, or other complications necessitating intensive care.

These criteria were adapted from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines to ensure consistency in patient categorization.

The COPD Assessment Test (CAT) scores, which measure the impact of COPD on patients' health status, were categorized into three grades based on the total score:

- **Grade 1** (Mild Impact): CAT score of 0–10, indicating a low impact of COPD on daily life.
- **Grade 2** (Moderate Impact): CAT score of 11–20, reflecting a moderate impact of COPD on daily activities and quality of life.
- **Grade 3** (Severe Impact): CAT score of 21 or higher, representing a high impact of COPD with significant impairment in daily life.

The combined Global Initiative for Chronic Obstructive Lung Disease (GOLD) assessment groups (A, B, C, D) were used to classify patients based on their symptoms and exacerbation history. For analysis purposes, these groups were numerically coded as follows:

- **Category 1:** GOLD Group A (Low symptoms, low risk of exacerbation).
- **Category 2:** GOLD Group B (High symptoms, low risk of exacerbation).
- **Category 3:** GOLD Group C (Low symptoms, high risk of exacerbation).
- **Category 4:** GOLD Group D (High symptoms, high risk of exacerbation).

Furthermore, data regarding systolic pulmonary artery pressure (SPAP) were extracted from the medical records. Pulmonary function was meticulously assessed using spirometry, with a focal point on the forced expiratory volume in one second (FEV1) and the FEV1 to forced vital capacity (FVC) ratio, which were also extracted from the patients' medical records.

Statistical Analysis

Data were analyzed using SPSS version 26 (IBM Corp., Armonk, NY, USA) and R software version 4.0.2. Descriptive statistics were used to summarize the sample characteristics, including frequencies, percentages, means, and standard deviations (SD). The normality of continuous variables was assessed using the kolmogorov-smirnov test. As the majority of the continuous variables were not normally distributed, non-parametric tests were used in the analysis. The correlation between NLR and various parameters were analyzed using Spearman's correlation coefficient (rho). A p-value less than 0.05 was considered statistically significant.

Results

Demographic Characteristics of Patients

In this study, we analyzed a cohort of 49 participants, all of whom were patients diagnosed with COPD. The participants had an average age of 62.3 (±8.70) years. The gender distribution leaned towards males, constituting 59% of the sample. In the context of occupation, the majority were housekeepers, making up 63% of the cohort. Analyzing lifestyle habits revealed that a significant portion of the participants were smokers, with 62% indulging in cigarettes and 37% preferring hookah. Furthermore, 37% were exposed to home bakery environments. Substance use was also significant, with 61% reporting opium use. On the clinical front, 22% had a history of IHD, 43% were managing HTN, and 12% had been diagnosed with DM (Table 1).

Clinical and Laboratory Parameters

In the current analysis encompassing 49 COPD patients, the mean NLR was found to be 2.1 (±1.46). The SBP and DBP were noted to be 124.7 (±14.16) mmHg and 80.6 (±6.59) mmHg, respectively. The SpO2 levels were documented at 92.6% (±1.85). Furthermore, the SPAP was 35.7 (±9.34) mmHg, RBC count was 5.0 (±0.30) x10^6/µL, Hb concentration was 16.7 (±18.79) g/dL, and PLT count was 257.9 (±113.14) x10^3/µL. The WBC count was 7.5 (±2.02) x10^3/µL, with Neut, Lym, Eos, and Baso percentages being 57.9% (±10.39), 41.2% (±45.37), 3.4% (±2.99), and 1.6% (±1.72), respectively. The biochemical tests revealed FBS levels of 97.6 (±22.89) mg/dL and ferritin levels of 119.0 (±88.70) ng/mL.

The correlation findings delineated in Table 2 were analyzed. The FEV1/FVC ratio exhibited a negligible negative correlation with NLR (rho = -0.03, p = 0.83), while FEV1 demonstrated a non-significant negative correlation (rho = -0.66, p = 0.65). The arterial blood gas analysis parameters, including pH and HCO3, showed slight correlations with NLR with rho values of 0.16 (p = 0.26) and <-0.01 (p = 0.96), respectively. PCO2 exhibited a weak negative correlation with NLR (rho = -0.07, p = 0.62). The echocardiographic parameter EF displayed a moderate negative correlation with NLR (rho = -0.30, p = 0.03). In the context of inflammatory markers, the analysis revealed that ESR exhibited a weak positive correlation with NLR (rho = 0.28, p = 0.04), whereas CRP demonstrated a weak negative correlation (rho = -0.24, p = 0.42). Furthermore, LDH levels indicated a negligible negative correlation with NLR (rho = -0.04, p = 0.76). Interestingly, ferritin levels also showed a slight negative correlation with NLR, with a rho value of -0.07 (p = 0.60).

Table 1. Demographic Characteristics of Patients.

Variable		N = 49[1]
Age (years)		62.3 (8.70)
Gender	**Male**	29 (59%)
	Female	20 (41%)
BMI (kg/m^2)		25.9 (1.69)
Smoking Habits	**Cigarette**	29 (62%)
	Hookah	18 (37%)
Home Bakery		18 (37%)
Substance Use (Opium)		30 (61%)
IHD		11 (22%)
HTN		21 (43%)
DM		6 (12%)

[1]Median (IQR) or Frequency (%).
IHD: Ischemic Heart Disease, **HTN:** Hypertension, **DM:** Diabetes Mellitus.

Compare NLR with COPD Clinical Assessment Scales

In the analysis presented in Table 3, the NLR was comparatively analyzed across various clinical assessment scales in the patients. A notable observation was in the AECOPD categories, where a significant difference was observed with a p-value of 0.04. The analysis indicates a significant relationship between NLR and AECOPD in categories 1 and 2, corresponding to mild and moderate exacerbations. However, no significant association was observed between NLR and category 3 (severe exacerbations). Particularly, there was a noticeable increase in NLR from category 0 (1.65 ±1.07) to category 2 (2.91 ±2.11). In the context of the Receiver Operating Characteristic (ROC) curve analysis for AECOPD, which is visually represented in Figure 1, the NLR exhibited a moderate diagnostic power with an area under the curve (AUC) of 0.68 (95% CI: 0.52-0.83). The ROC curve further demonstrated a sensitivity of 0.67 and a specificity of 0.71, with a corresponding NLR value of 1.67.

The mMRC Dyspnea Scale, GOLD Spirometry Classification, and GOLD Combined Assessment scales showed non-significant variations in NLR across their respective categories (p-values of 0.75, 0.99, and 0.97 respectively). The mean CAT score was recorded as 19.4 (±4.80), although the CAT grade analysis did not reveal a significant association with NLR (p-value of 0.85).

Discussion

This study, a prospective cohort study involving 49 COPD patients, primarily male with an average age of 62.3 years, investigated the role of NLR in COPD patients, revealing a mean NLR of 2.1. The study identified a moderate negative correlation between EF and NLR and a weak positive link between ESR and NLR. The study also highlighted a significant increase in NLR in higher AECOPD categories, suggesting its potential as a marker for exacerbation severity.

Table 2. Correlation Analysis of Various Clinical, Hematological, and Biochemical Parameters with NLR in COPD Patients.

Variable	N = 49[1]	r[2]	P value[3]
Pulmonary Function Tests			
FEV1/FVC Ratio	64.0 (10.35)	-0.03	0.83
FEV1	57.2 (12.39)	-0.66	0.65
FVC	64.8 (9.46)		
Arterial Blood Gas Analysis			
pH	7.4 (0.03)	0.16	0.26
HCO3 (mmol/L)	31.5 (28.45)	<-0.01	0.96
PCO2 (mmHg)	45.8 (5.52)	-0.07	0.62
Echocardiographic Parameters			
EF (%)	53.6 (3.82)	-0.30	0.03
SPAP (mmHg)	35.7 (9.34)	0.26	0.30
Inflammatory Markers			
ESR (mm/hr)	15.2 (11.58)	0.28	0.04
CRP (mg/L)	8.2 (8.87)	-0.24	0.42
LDH (U/L)	309.0 (55.33)	-0.04	0.76
Ferritin (ng/mL)	119.0 (88.70)	-0.07	0.60

[1]Median (IQR) or Frequency (%), [2] Spearman's rank correlation coefficient, [3] Spearman's test.

FEV1: Forced Expiratory Volume in 1 second, **FVC:** Forced Vital Capacity, **HCO3:** Bicarbonate, **PCO2:** Partial Pressure of Carbon Dioxide, **EF:** Ejection Fraction, **SPAP:** Systolic Pulmonary Artery Pressure, **ESR:** Erythrocyte Sedimentation Rate, **CRP:** C-Reactive Protein, **LDH:** Lactate Dehydrogenase, **NLR:** Neutrophil-to-Lymphocyte Ratio.

Table 3. Comparative Analysis of NLR Across Various COPD Clinical Assessment Scales.

Variable	N = 49 Frequency (%)	NLR Mean (SD)	P value[1]
mMRC			0.75
Grade 0	5 (10%)	1.88 (0.99)	
Grade 1	16 (33%)	2.29 (1.63)	
Grade 2	24 (49%)	2.08 (1.58)	
Grade 3	4 (8.2%)	1.75 (0.25)	
AECOPD			0.04
Category 0	21 (43%)	1.65 (1.07)	
Category 1	17 (35%)	2.13 (1.19)	
Category 2	11 (22%)	2.91 (2.11)	
GOLD			0.99
Grade 2	33 (67%)	2.09 (1.35)	
Grade 3	14 (29%)	2.18 (1.81)	
Grade 4	2 (4.1%)	1.69 (0.49)	
CAT Grade			0.85
Grade 1	3 (6.1%)	1.58 (0.31)	
Grade 2	25 (51%)	2.16 (1.32)	
Grade 3	21 (43%)	2.10 (1.72)	
GOLD Combined			0.97
Category 1	2 (4.1%)	1.74 (0.18)	
Category 2	31 (63%)	2.11 (1.40)	
Category 4	16 (33%)	2.12 (1.69)	

[1] Independent-Samples Kruskal-Wallis Test.

mMRC: Modified Medical Research Council, **COPD**: Chronic Obstructive Pulmonary Disease, **AECOPD:** Acute Exacerbations of Chronic Obstructive Pulmonary Disease, **GOLD:** Global Initiative for Chronic Obstructive Lung Disease.

Numerical representation of Combined GOLD categories: **1 = Group A**, **2 = Group B**, **3 = Group C**, 4 = Group D.

The Shao et al. study (7) also highlighted the potential of NLR as a predictive marker for clinical outcomes and readmission risks among AECOPD patients, with a higher optimal cut-off value of 4.43. However, the cut-off value identified in this study (1.67) is considerably lower than that identified, suggesting a potential difference in the severity of the patient populations studied or possibly a regional variation. Similarly, the Zinellu et al. meta-analysis (8) involving 10,038 patients across 15 studies echoed the potential utility of NLR in early risk stratification and management of AECOPD patients, with significant associations with adverse outcomes.

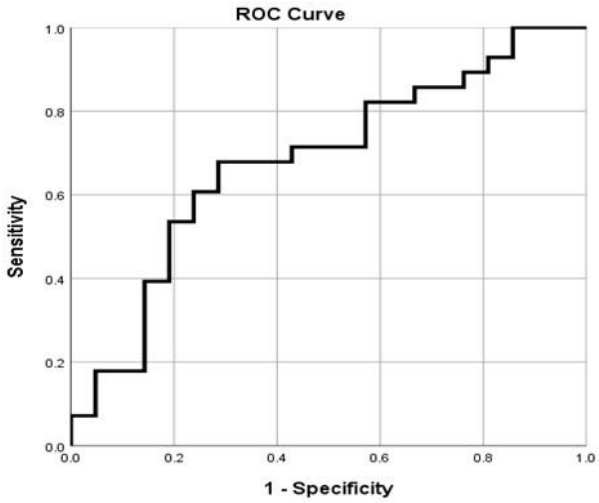

Figure 1. ROC Curve Analysis for NLR as a Predictor of Exacerbations in COPD Patients. AUC: 0.68 (95% CI: 0.52-0.83) An optimal cutoff value of 1.67, the NLR demonstrates a sensitivity of 0.67 and a specificity of 0.71.

The Ardestani et al. (9) further substantiated the prognostic value of NLR, establishing a significant relationship with primary markers like ESR and CRP. The Hedhliabir et al. (10) study emphasized the correlation of NLR and PLR with severity and outcomes of AECOPD, associating higher levels with poor prognosis. Moreover, previous studies (11, 12) explored the role of these biomarkers in predicting pulmonary hypertension and acute exacerbation in COPD patients, respectively, further accentuating the potential of NLR as a significant biomarker in COPD management.

In the realm of cardiac function assessment, NLR delved into the combined predictive value of NLR and platelet-to-lymphocyte ratio (PLR) in foretelling cardiac mortality in patients suffering from acute decompensated heart failure with preserved EF, establishing that elevated NLR and PLR values were independently linked to cardiac death (13). In the context of patients with heart failure with preserved ejection fraction (HFpEF), the NLR has been identified as an autonomous predictor for the onset of heart failure (HF), with other markers such as lymphocyte-to-monocyte ratio (LMR), fibrinogen-to-albumin ratio (FAG), monocyte to high-density lipoprotein ratio (MHR), albumin to globulin ratio (AGR), and N-terminal pro b-type natriuretic peptide (NT-proBNP) emerging as independent predictors for an escalated New York Heart Association (NYHA) functional class (14). Furthermore, research exploring the interrelation between plasma osmolality and NLR in heart failure patients deduced that augmented NLR values might be synonymous with increased plasma osmolality, potentially signaling an intensified inflammatory state in the heart failure phenomenon (15). Lastly, a study examining the interplay between subclinical left ventricular ejection fraction (LVEF) and platelet-to-lymphocyte ratio (PLR) in individuals undergoing peritoneal dialysis revealed a negative correlation between LVEF and both PLR and monocyte-to-lymphocyte ratio (MLR) (16).

The generalizability of this study is somewhat limited due to a smaller sample size and regional focus, potentially restricting the applicability of the findings to a broader population. This limitation, encompassed a larger sample size across multiple studies, providing a more robust evidence base for the association between NLR and adverse outcomes in AECOPD patients.

Furthermore, the reliance on personal interviews and medical records for data collection in this study could introduce information bias, potentially affecting the validity of the findings. This aspect contrasts with the methodologies employed in the other studies, which utilized more extensive datasets and retrospective analyses, potentially offering a more comprehensive view of the associations between NLR and COPD outcomes.

Conclusion

In our investigation, there is a moderate negative correlation between the NLR and EF which suggests that an increased NLR might be indicative of reduced cardiac efficiency. Furthermore, a weak positive correlation was observed between the ESR and NLR which possibly serving as a marker for monitoring disease progression and response to treatment. NLR may serve as a marker for mild to moderate exacerbations in COPD patients (categories 1 and 2); however, its predictive value for severe exacerbations (category 3) remains unclear. Further research is needed to explore the underlying mechanisms and its utility across the full spectrum of exacerbation severity.

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