Original Article

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TANAFFOS

Could We Predict Chronic Obstructive Pulmonary Disease Exacerbation Based on Neutrophil to Lymphocyte Count Ratio (NLR)?

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Background: The neutrophil to lymphocyte ratio (NLR) is an inflammatory biomarker that could be used as an indicator of systemic inflammation (sepsis) and could also be used to predict the prognosis of some diseases, such as solid cancer, community pneumonia, as well as cardiovascular diseases. This study aimed to assess the potential role of NLR and eosinopenia in patients with acute exacerbation of COPD (AECOPD) compared to those in the stable phase of the disease.

Materials and Methods: NLR was assessed and compared in patients with AECOPD (n=92) and those in the stable phase of COPD (n=240). Patients under the age of 18, those who used inhaled corticosteroids, or those with any condition affecting the neutrophil (NEU) or lymphocyte (LYM) count in peripheral blood, such as hematological illnesses, pregnancy, or a history of medication use, were excluded from the study. The NLR was determined using NEU and LYM counts from regular blood tests. We defined the cut-off value for eosinopenia as the percentage of eosinophils≤1%.

Results: We included 332 inpatients with COPD diagnosed in our hospital from April to October 2021. AECOPD was discovered in 92 patients. Patients with exacerbation had considerably lower levels of BMI (24.32±4.38 vs 26±4.02), FEV1/FVC (55.38±9.14 vs 60.54±6.95), and NLR ratio, except for the first NLR quartile (39.13 %), the second was 20.65 %, the third was 18.48 %, and the fourth was 21.74 %. Eosinopenia was detected in 79 (85.87 %) of AECOPD patients.

Conclusion: We found that the NLR was lower in patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD), except for those in the first NLR quartile.

Keywords: NLR, COPD; Eosinopenia; Acute Exacerbation

INTRODUCTION

According to data from the World Health Organization (WHO), chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide, with around 3.23 million deaths in 2019. More than 80% of these deaths happened in low and middle-income countries (1). In COPD, chronic inflammatory response can provoke parenchymal tissue destruction (emphysema) and interruption of normal repair and defense mechanisms which can result in small fibrosis (2). COPD is characterized by increased numbers of macrophages, increased neutrophil activation, and increased lymphocytes that include Th1, Th17, ILC3, and Tc1 cells. In general, systemic inflammation may have a role in various comorbid diseases associated with COPD (3). The neutrophil to lymphocyte ratio (NLR) is an inflammatory

biomarker that could be used as an indicator of systemic inflammation (sepsis) and could also be used to predict the prognosis of some diseases such as solid cancer (lung, colorectal, pancreatic, breast, gastric, and ovarian), community pneumonia, and cardiovascular outcomes. Even though COPD is a chronic inflammatory disease, there has been little research on the involvement of NLR in individuals with COPD (4, 5).

The purpose of this study was to assess the potential role of NLR and eosinopenia in patients with acute exacerbation of COPD (AECOPD) in comparison to those in the stable phase of the disease.

MATERIALS AND METHODS

We included 332 inpatients with COPD diagnosed in our hospital between April to October 2021. This study was authorized by the institutional review board (University Clinical Center "Zemun," approval notice number: 2000/13) and was carried out following the Helsinki Declaration. During the 6 months, 92 of 332 patients developed AECOPD, which is usually defined as an increase in shortness of breath, cough intensity, quality, and/or increase in oxygen requirements. When the patient's condition stabilized and following discharge from the outpatient department, the clinician determined the AECOPD convalescence duration. Patients with stable COPD were eligible if they had no history of acute exacerbation in the previous 6 months and were not on long-term oxygen therapy or regular oral corticosteroids. According to the Global Initiative for Chronic Obstructive Pulmonary Disease, COPD was diagnosed by spirometry if the forced expiratory volume in the first second to forced vital capacity ratio (FEV1/FVC) was less than 0,7. Exclusion criteria were as follows: Patients under the age of 18, those who used inhaled corticosteroids, those with any condition affecting the NEU or LYM counts in peripheral blood such as hematological illnesses, pregnancy, or a history of medication use (e.g., granulocyte colony-stimulating factor). In our study, patients with granulocytic insufficiency induced by non-inflammatory causes were not included. The NLR was determined using NEU and LYM counts from routine blood tests. We defined the cut-off value for eosinopenia as the percentage of eosinophils ≤1% (6,7).

Statistical analysis

Statistica version 8 was used for the statistical analysis (StatSoft Inc, 2007). Pearson's chi-squared test ($\chi 2$) was utilized to assess the distribution between groups. The Shapiro–Wilk test was used to determine the normality of continuous variable distributions. For continuous variables, appropriate tests were used depending on the distribution: Student's t-test for variables with normal distribution, non–parametric Man–Whitney U test, and Kruskal–Wallis Anova for variables with skewed distribution. Logistic regression analysis was utilized to assess the strength of the link; the results were presented as odds ratios (OR) with 95 % confidence intervals (95% CI). Multiple regressions were used to predict the outcome of a response variable based on the analysis of several explanatory variables. As a nonparametric correlation test, Kendall's rank correlation was performed. P values of ≤0.05 were regarded as statistically significant.

RESULTS

This prospective study comprised enrolled COPD patients, 92 of whom had an exacerbation at least once during the 6-month follow-up period. Table 1 displays the demographic and clinical characteristics of the study participants. Patients with exacerbation of COPD were predominantly women and were significantly more likely to be in disease stage 3 compared to those without exacerbation. Patients with exacerbation also had significantly lower BMI, FEV1/FVC, and NLR ratio levels (Table 1). Eosinophil levels were also substantially lower among patients with exacerbation, and eosinopenia (defined as eosinophil level ≤1%) was significantly more common among COPD exacerbation patients.

Association analysis

This study looked at the relationship between NLR and COPD exacerbations in patients with COPD. NLR values

were classified into four groups based on quartiles. Table 2 displays the values of the quartile distribution. The Pearson's chi-squared test revealed a significant relationship between quartiles (p=0.01). In Table 3, we showed the distribution of clinical characteristics regarding the quartiles among patients with COPD. Because patients in the first NLR quartile range were the most common in the exacerbation group, we analyzed the results by categorizing patients in the first versus the other three quartiles. Patients in the upper quartiles are more common among COPD patients without exacerbation, indicating a protective effect (unadjusted OR=0.41, 95% CI=0.24–0.70, p=0.001) (Table 4).

Table 1. The clinical characteristics of patients included in the study were separated into groups with regard to the presence of exacerbations during the six-month follow-up

Characteristic	No exacerbation n=240	Exacerbation n=92	P
Gender, F (%)	103 (42.93)	56 (60.87)	0.03*
Smokers (%)	173 (72.08)	63 (68.48)	0.51*
Stadium 2/3 (%)	212/28 (88.33/11.67)	61/31 (66.30/33.70)	<0.001*
Age, years	62.81±10.09	62.90±9.84	0.89#
BMI, kg/m2	26±4.02	24.32±4.38	0.002#
FVC, %	74.37±19.64	75.87±19.97	0.53 m#
FEV1, %	48.44±16.32	46.04±19.35	0.25 #
FEV1/FVC, %	60.54±6.95	55.38±9.14	<0.001#
WBC (10^9)	8.61±2.08	8.87±2.35	0.50#
Neutrophil, %	72.74±11.83	69.79±12.31	0.01#
Lymphocyte, %	18.43±8.70	21.16±9.63	0.02#
NLR	6.12±6.63	5.51±5.36	0.06 #
Eosinophil, %	0.88±1.20	0.59±1.26	0.003#
Eosinopenia (%)	174 (72.5)	79 (85.87)	0.01*

F: females; NLR: neutrophil to lymphocyte ratio; FVC: Forced vital capacity; FEV1: forced expiratory volume in one second; *Pearson's chi-squared test; # Mann–Whitney U–test; FVC –; FEV1 –; continuous variables are presented as mean ± standard deviation; values are considered significant at p ≤ 0.05.

After adjusting for age, gender, BMI, smoking status, FEV1/FVC, and eosinopenia, the result remained significant (OR=0.40, 95% CI=0.22–0.72, p=0.002; Table 4). Multiple regression analysis revealed that BMI, FEV1/FVC, eosinopenia, and NLR were significant contributing factors to exacerbation occurrence (Table 5). In a separate study, eosinopenia was found to be highly linked with exacerbation (OR=2.30, 1.20–4.41, p=0.011). Kendall's rank correlation tau identified a substantial relationship between NLR and eosinophil percent count: τ=–0.17 (p<0.000001). Furthermore, we looked at NLR associations in the same model (1st versus 2nd–4th quartile) and only in patients with eosinopenia. Patients in quartiles 2-4 were significantly less common among exacerbated (63.29%) compared to those who were exacerbation-free (83.33%), as shown in Table 6 (OR=0.34, 1.18–0.63, p=0.0006).

After accounting for additional confounding factors (age, gender, BMI, smoking status, and FEV1/FVC), the outcome was still statistically significant, with OR=0.42, 95 % CI=0.21–0.83, and p=0.011 (Table 6). We looked into the relationship between NLR and disease stadiums. The patient groups were divided by the median in the analysis. The upper two quartiles were considerably less prevalent in disease stadium 3 (37.29 %) compared to disease stadium 2 (52.38 %), indicating a protective effect against disease progression. Logistic regression analysis revealed a significant and independent correlation with p=0.038 and adjusted OR=0.53, with a 95% CI = 0.29–0.97 (Table 7).

Table 2. Comparison of NLR stratified by quartiles with regard to exacerbation occurrence within six - months period, among patients with COPD.

Quartile	NLR range	Patients	Patients without exacerbation	Patients with exacerbation	P (χ2)
		n=332 (%)	n=240 (%)	n=92 (%)	
1	≤ 2.53	87 (24.62)	51 (21.25)	36 (39.13)	0.01
2	2.53–3.85*	80 (25.53)	61 (25.42)	19 (20.65)	
3	3.85*–5.75	82 (24.92)	65 (27.08)	17 (18.48)	
4	> 5.75	83 (22.92)	63 (26.25)	20 (21.74)	

NLR – neutrophil to lymphocyte ratio; p (χ^2) – Pearson's chi-squared test; * value of the median; values are considered significant at p ≤ 0.05.

Table 3. Distribution of clinical characteristics regarding quartiles, among patients with COPD.

Characteristic	Quartile 1 n = 87	Quartile 2 n = 80	Quartile 3 n = 82	Quartile 4 n = 83	P
Exacerbation	36 (39.31)	19 (20.65)	17 (18.48)	20 (21.74)	0.034*
Gender, f (%)	34 (39.08)	43 (53.75)	50 (60.98)	46 (55.42)	0.029*
Smokers, (%)	59 (67.82)	61 (76.25)	61 (74.39)	55 (66.27)	0.41*
Stadium 2/3 (%)	71(26.01)/16(27.12)	59(21.61)/21(35.59)	78(28.57)/4(6.78)	65(23.81)/18(30.51)	0.003*
Age, years	63.55±12.30	62.51±10.36	63.89±7.07	61.24±9.22	0.36#
BMI kg/m²	25.05±4.14	25.66±4.00	25.56±4.15	25.85±1.13	0.69#
FVC (%)	75.99±19.84	74.25±14.96	74.83±20.96	74.63±23.39	0.93#
FEV1 (%)	47.98±17.56	46.84±16.40	50.35±18.47	46.7±17.90	0.38#
FEV/FVC(%)	58.74±8.29	57.74±9.41	62.19±5.41	58.59±7.69	0.01#
WBC (10^9)	10.55±15.14	10.72±12.84	9.08±2.06	9.2±2.22	<0.001#
Neutrophil (%)	58.67±5.48	68.66±5.41	75.30±7.08	85.61±8.67	<0.001#
Lymphocyte (%)	30.74±4.90	21.56±2.28	15.81±2.26	8.1±3.42	<0.001#
NLR	1.97±0.42	3.21±0.37	4.82±0.56	13.56±8.60	<0.05#
Eosinophil (%)	0.92±1.18	1.18±1.69	0.86±0.98	0.26±0.64	<0.001#
Eosinopenia (%)	58 (22.92)	56 (22.13)	61 (24.11)	78 (30.78)	0.0001*

* Pearson's chi–squared test; #Kruskal–Wallis Anova; FVC – Forced Expiratory Volume; FEV1 – Forced expiratory volume in the first second; NLR – neutrophil to lymphocyte ratio; continuous variables are presented as mean ± standard error; values are considered significant at p ≤ 0.05.

Table 4. Association of NLR quartiles with the presence of exacerbations within six months, among patients with COPD.

NLR quartile	Exacerbation no n=87 (%)	Exacerbation yes n=245 (%)	OR	95% CI	P
1	51 (21.25)	36 (39.13)	1		
2–4	189 (78.75)	56 (60.87)	0.41	0.24–0.70	0.001
			0.40	0.22–0.72	0.002*

NLR – neutrophil to lymphocyte ratio; OR – odds ratio; CI – confidence interval; * Adjusted for age, gender, BMI, smoking status, FEV1/FVC, and eosinopenia; values are considered significant at p ≤ 0.05.

Table 5. Multivariate regression analysis of exacerbation status regarding confounding factors and NLR.

Factors	β	± SE (β)	B	± SE (B)	P
Gender	–0.060	0.054	–0.050	0.049	0.273
Age	0.002	0.053	0.000	0.002	0.961
BMI	–0.118	0.052	–0.012	0.005	0.025
Smoking	0.083	0.053	0.082	0.052	0.117
FEV1/FVC	–0.264	0.053	–0.014	0.003	0.000
Eosinopenia	–0.159	0.052	–0.167	0.054	0.002
NLR*	–0.162	0.052	–0.165	0.053	0.002

*NLR is distributed into quartiles and analysis is conducted in relation to upper and lower quartiles (quartile 1–2 vs. quartile 3–4); β – standardized beta; B – unstandardized beta; SE – standard error; values are considered significant at p ≤ 0.05.

Table 6. Association of NLR quartiles with the presence of exacerbations within six months, among patients with COPD and eosinopenia.

NLR quartile	Exacerbation no n=87 (%)	Exacerbation yes n=245 (%)	OR	95% CI	P
1	29 (16.67)	29 (36.71)	1		
2–4	145 (83.33)	50 (63.29)	0.34	0.18–0.63	0.0006
			0.42	0.21–0.83	0.011*

NLR – neutrophil to lymphocyte ratio; OR – odds ratio; CI – confidence interval; * Adjusted for age, gender, BMI, smoking status, and FEV1/FVC; values are considered significant at p ≤ 0.05.

Table 7. Association of disease stadium with NLR quartiles among patients with COPD

NLR quartile	Disease stadium 2 n=273 (%)	Disease stadium 3 n=59 (%)	OR	95% CI	P
1–2	130 (47.62)	37 (62.71)	1		
3–4	143 (52.38)	22 (37.29)	0.54 0.53#	0.30–0.96 0.29–0.97#	0.037 0.038#

NLR – neutrophil to lymphocyte ratio; OR – odds ratio; CI – confidence interval; * Adjusted for age, gender, BMI, smoking status, and FEV1/FVC; # Adjusted for age, BMI, and smoking status; values are considered significant at $p \leq 0.05$.

DISCUSSION

According to our findings, nearly 28% of participants had AECOPD, with females being significantly more affected than males (60.87%). Patients with AECOPD were younger than those without exacerbation and had significantly lower BMI, FEV1/FVC, and NLR ratio levels. We could not find studies where NLR ratio levels were significantly lower in patients with AECOPD, we only found that in nonalcoholic fatty liver disease (NAFLD) NLR ratio level is low (5). A study conducted in South Korea involved 144 patients, 40% of whom had acute exacerbations of chronic obstructive pulmonary disease (AECOPD). The study primarily included male patients, and the participants were older than those in our study. Additionally, the body mass index (BMI) and forced expiratory volume in one second to forced vital capacity (FEV1/FVC) ratios were not significantly different between patients with AECOPD and those with stable chronic obstructive pulmonary disease (COPD). However, the neutrophil-to-lymphocyte ratio (NLR) was significantly higher in the AECOPD patients (6). Eosinopenia was seen in a high proportion of our AECOPD patients (85.87%). Some authors monitored eosinophil count in AECOPD and discovered that 32.34 % of 235 respondents had eosinopenia, concluding that eosinopenia is associated with a high risk of treatment failure and in-hospital mortality (8, 9), whereas others described longer hospitalization, rehospitalization, and the need for mechanical ventilation in AECOPD patients (10). Following that, we divided the NLR ratio into four groups based on quartiles. The results showed that patients in the first NRL quartile were the most common in AECOPD; however, when comparing the first and other quartiles, individuals in the upper quartiles were more common among stable COPD patients. Patients in quartiles 2-4 were statistically substantially less common among patients with exacerbation compared to exacerbation-free patients, and the result remained statistically significant after adjusting for other confounding factors (age, gender, BMI, smoking status, and FEV1/FVC).

Some authors conducted a study in which they enrolled 885 participants and investigated the relationship between NLR count ratio and airflow limitation and exacerbation throughout the first year of follow-up and the preceding year based on NLR quartiles ($Q \leq 11.43$, $1.43 < Q2 \leq 2.04$, $2.04 < Q3 \leq 2.94$, and $2.94 < Q4$). Ultimately, they discovered that participants with greater NLR were more likely to have a shorter 6-min walk distance test and that as the NLR quartile increased, the values of FEV1, FVC, and FEV1/FVC considerably deteriorated. After adjusting for age, gender, BMI, pack-years of smoking, and inhaled corticosteroids, NLR values were found to be inversely related to the severity of airway restriction measured by FEV1 (11).

What function does the NLR ratio have in severe AECOPD and clinical outcomes? In their study, the Chinese researchers evaluated 604 individuals with AECOPD. All participants who had two or more exacerbations were placed in the group with frequent exacerbations. Their findings revealed that the group with

frequent exacerbations had higher levels of NLR (5.93 vs. 4.41) and a greater incidence of poor outcomes (59 vs. 38) than the group with infrequent exacerbations (12). Furthermore, we discovered five additional studies in which authors stated that NLR is significantly higher in patients who died in the hospital and that the NLR predictor of in-hospital death varies and ranges from 3.3 to ≥16 (13-17). Exploring the relationship between NLR ratio and disease stadium, we discovered that the upper two quartiles were considerably less prevalent in disease stadium 3 compared to disease stadium 2, indicating a protective effect against disease development. According to GOLD, several Turkish investigators included 476 patients with AECOPD and COPD in a stable phase. They discovered that the NLR ratio was higher in patients with AECOPD compared to COPD in the stable phase and control group. They also discovered that there was a linear increase in NLR with COPD severity in the stable group, but this increase was not linear in patients with exacerbation in a way that NLR tended to be high in stage 1. This increase was not statistically significant, and NLR was higher in patients in stage 4 than in patients in stages 2 and 3 (18).

CONCLUSION

Our study found that the Neutrophil-to-Lymphocyte Ratio (NLR) was lower in patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD), except for those in the first NLR quartile. Additionally, when we examined the relationship between the NLR ratio and disease stage, we discovered that the upper two quartiles were significantly less frequent in stage 3 compared to stage 2, suggesting a protective effect against disease progression. We were unable to find any studies that indicated a low NLR ratio in AECOPD patients. Moreover, eosinopenia was notably higher among those with AECOPD. The NLR shows promise as a potential biomarker for COPD, although research in this area remains quite challenging. Further detailed studies are necessary, especially regarding eosinopenia in COPD patients.

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