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Original Article

Utility of neutrophil to lymphocyte ratio in the prediction of inflammation and COPD mortality

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Abstract

Introduction: The Neutrophil-to-Lymphocyte Ratio (NLR) has been utilized to predict clinical outcomes in cardiovascular diseases, infectious diseases, and solid tumors and it has a potential association with the severity of Chronic Obstructive Pulmonary Disease (COPD). This study aimed to determine whether NLR is a possible predictor of inflammation severity and mortality in COPD.

Methodology: A prospective analysis of NLR in 70 COPD patients, and its relation with biochemical, lung function parameters, and mortality was assessed.

Results: NLR was negatively associated with oxygen saturation ($p < 0.05$) and positively related to C-reactive protein (CRP) ($p < 0.05$), matrix metalloproteinase-9 (MMP-9) ($p \leq 0.001$), tissue inhibitor of metalloproteinase-1 (TIMP-1) ($p < 0.05$), MMP-9/TIMP-1 ratio ($p < 0.05$), and the modified Medical Research Council dyspnea scale (mMRC) score ($p < 0.05$). Deceased patients had significantly higher NLR ($p < 0.05$). Older age and lower levels of saturation were independently associated with higher mortality in COPD patients ($p < 0.05$).

Conclusions: NLR in COPD correlates with inflammation and protease/antiprotease balance, with elevated NLR detected in deceased patients. These findings suggest that NLR can be a helpful clinical marker in COPD.

Key words: Neutrophil-to-Lymphocyte Ratio; inflammation; mortality; COPD.

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Introduction

Chronic obstructive pulmonary disease (COPD) presents a global health concern with a prevalence of 10.6% [1]. It is also the third leading cause of mortality, with an estimated three million deaths annually [2]. In addition to persistent airway limitation and chronic airway inflammation, COPD is characterized by systemic inflammation [3]. While COPD is typically classified based on lung function parameters (GOLD stage I-IV), particularly forced expiratory volume in 1 second (FEV_1), it is now widely recognized that FEV_1 does not fully reflect the complexity of the disease [4]. Previous research has identified several biomarkers [5–8] that correlate with inflammation severity and increased risk of death in COPD patients, although the majority is not used in routine clinical practice.

The Neutrophil-to-Lymphocyte Ratio (NLR), a novel inflammatory marker, has generated significant interest recently. This index, derived from a commonly performed test (complete blood count), offers easy accessibility and cost-effectiveness in clinical practice, making it a promising tool for predicting clinical outcomes in various conditions. NLR has already been used to predict clinical outcomes in cardiovascular diseases [9], solid tumors [10], and infectious conditions [11]. When it comes to COPD, NLR is higher in exacerbations than in stable patients, suggesting a potential link to disease severity [12]. Moreover, some authors have suggested that NLR could be more precise than conventional and costly markers. These findings underscore the novelty and potential of NLR in COPD research, highlighting further interest and potential applications in clinical practice.

This study aimed to determine whether NLR is a possible predictor of inflammation severity and mortality in COPD.

Methodology

Study population and demographics

This study presents a prospective analysis of NLR in 70 COPD patients, examining its relation with biochemical markers, lung function parameters, and mortality outcomes. It was conducted at the hospital-based outpatient pulmonology department in the Clinical Center of Serbia (Belgrade) between May 2017 and January 2018. The diagnosis was established according to the Global Initiative for Chronic Obstructive Disease (GOLD) [13], not six months before enrollment. Patients over 40 years old, whose disease was stable for at least four weeks, were included.

Age, sex, smoking status, self-reported comorbidities, inhalation therapy, and AECOPD reported as events per year were initially recorded. Symptoms were assessed by the Modified Medical Research Council Dyspnea Scale (mMRC). COPD exacerbation was defined as the acute worsening of respiratory symptoms that resulted in the requirement for additional treatment. A frequent exacerbator was described as a COPD patient with ≥ 2 exacerbations per year [14]. Subjects were stratified according to NLR value as high and low groups using a cut-off value of 3.34 as previously described [15].

Mortality data were collected via phone call five years after the enrollment of the first patient. Data on survival were self-reported or reported by family members.

Blood sampling

Blood samples were collected and analyzed for complete blood count (CBC) and white blood cell count (WBC) using a Beckman Coulter Hematology Analyzer. The Neutrophil-to-Lymphocyte Ratio (NLR) was calculated by dividing the number of neutrophils by the number of lymphocytes. After collecting whole blood using Vacutainer tubes, the samples were stored undisturbed at room temperature for 30 minutes before being centrifuged at 1000 × g for 10 minutes. Following centrifugation, the serum samples were divided into 0.5 mL portions and stored at -80 °C until analysis. MMP-9 and TIMP-1 levels were assessed using enzyme-linked immunosorbent assay (ELISA) kits by the manufacturer's instructions (Quantikine ELISA, R&D Systems, Minneapolis, USA).

Pulmonary function tests

The functional assessments were conducted in accordance with the criteria established by the American Thoracic Society and the European Respiratory Society (ATS/ERS) [16,17]. Post-bronchodilator spirometry was performed using the JAEGER® MasterScreen Pneumo, and single-breath diffusion capacity for carbon monoxide (CO) using the JAEGER® MasterScreen Diffusion. The parameters analyzed were FEV_1, Forced Vital Capacity (FVC), the FEV1/FVC ratio, diffusion capacity for carbon monoxide (DLCO), and carbon monoxide transfer coefficient (KCO).

Table 1. Characteristics of the study cohort and according to the level of NRL.

Characteristic	Total (n = 70)	NLR		p^*
		< 3.34 (n = 47)	> 3.34 (n = 23)	
Basic characteristics				
Age, mean ± sd	68.14 ± 8.85	66.51 ± 7.49	71.48 ± 10.54	**0.026**[§]
Male, n (%)	37 (52.9)	25 (53.2)	12 (52.2)	0.936[€]
Female, n (%)	33 (47.1)	22 (46.8)	11 (47.8)	
BMI, mean ± sd	26.24 ± 5.41	26.55 ± 5.51	25.61 ± 5.26	0.496[§]
Current smoker, n (%)	25 (35.7)	17 (36.2)	8 (34.8)	0.909[€]
CVD comorbidities, n (%)	37 (52.9)	22 (46.8)	15 (65.2)	0.147[€]
COPD clinical parameters				
Number of exacerbations ≥ 2, n (%)	46 (65.7)	31 (66.0)	15 (65.2)	0.951[€]
mMRC score, med (min-max)	2 (0-4)	2 (0-4)	3 (0-4)	0.086[¥]
CRP, med (min-max)	3.1 (0.2-30.3)	2.5 (0.2-30.3)	5.7 (0.6-22.7)	0.175
MMP-9 (ng/ml), med (min-max)	892.34 (19.28-2139.44)	766.38 (19.28-1648.16)	1203.39 (177.23-2139.44)	**0.015**
TIMP-1 (ng/ml), med (min-max)	236.59 (112.50-445.73)	227.05 (112.50-445.23)	243.64 (157.50-360.23)	0.125[¥]
MMP-9/TIMP-1 ratio, med (min-max)	3. 48 (0.11-10.11)	3.19 (0.11-10.11)	4.72 (1.12-8.98)	0.052[¥]
Hgb (g/L), mean ± sd	146.76 ± 13.36	146.47 ± 12.78	147.35 ± 14.76	0.797[§]
Eosinophils, med (min-max)	0.19 (0.00-0.90)	0.20 (0.00-0.90)	0.15 (0.00-0.80)	0.302[¥]
Lung function parameters				
FEV1%, mean ± sd	44.03 ± 15.20	44.87 ± 15.08	42.30 ± 15.64	0.511[§]
FVC%, mean ± sd	85.96 ± 18.98	84.98 ± 16.77	87.96 ± 23.15	0.541[§]
FEV1/FVC, mean ± sd	41.33 ± 11.05	42.54 ± 10.85	38.87 ± 11.30	0.195[§]
SAT%, mean ± sd	93.67 ± 3.55	94.30 ± 3.74	92.39 ± 2.79	**0.034**[§]
DLCO%, mean ± sd	48.43 ± 18.60	50.33 ± 17.93	44.45 ± 19.76	0.226[§]
KCO%, mean ± sd	56.40 ± 22.14	58.13 ± 21.19	52.87 ± 24.07	0.355[§]

[*]for the level of significance of 0.05 according to [§]Student t test for two independent samples, [¥]Mann-Whitney test, and [€]Chi-square test.

Statistical analysis

The study summarized numeric data using mean and standard deviation or median and range, based on the normality of distribution. Normality assessment utilized the Shapiro-Wilk test and box plots. Categorical data were described through absolute and relative percentages. Comparisons between groups concerning numerical variables were performed using the Student *t*-test or Mann-Whitney test, contingent upon normality. For categorical data, the Chi-square test was applied. The association between parameters and NLR was evaluated using Spearman's rank correlation coefficient. Univariate and multivariate logistic regression analyses were conducted employing the enter method to identify factors related to mortality in COPD patients. Odds ratios (OR), 95% confidence intervals (95% CI) of OR, and *p* were reported. Statistical significance was set at a confidence level of 0.05. Analyses were conducted utilizing IBM SPSS ver. 26.

Study approval

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Ethics Committee of University Clinical center of Serbia (No. 81/22; the 24th of March 2016). Informed written consent was obtained from all subjects involved in the study.

Results

A total of 70 COPD patients with an average age of 68.14 ± 8.85 years with equal distribution of genders were included in this study. All evaluated characteristics of the study cohort, when stratified according to NLR value as high and low groups, are presented in Table 1. A third of subjects were smokers, and over 50% of them had some cardiovascular comorbidity. 23 (33%) subjects had elevated NLR values. Subjects with elevated NLR values were significantly older ($p = 0.026$), with higher MMP-9 ($p = 0.015$) and lower oxygen saturation ($p = 0.034$).

Furthermore, the evaluation was conducted on the association between the described characteristics and NLR in patients with COPD. A negative moderate association was found between NLR and saturation ($\rho = -0.313$, $p = 0.008$). Additionally, there was a moderate positive association between NLR and CRP ($\rho = 0.252$, $p = 0.035$, Figure 1), MMP-9 ($\rho = 0.419$, $p < 0.001$, Figure 2), TIMP-1 ($\rho = 0.292$, $p = 0.017$) MMP-9/TIMP-1 ($\rho = 0.294$, $p = 0.017$), and mMRC score ($\rho = 0.297$, $p = 0.012$), respectively.

Twenty-one subjects (30%) had died in the observed period. When subjects were stratified based on patient outcomes into survival and death groups, deceased patients had significantly higher NLR than those who didn't (3.257 vs. 2.320, $p = 0.044$). Also, these patients had lower diffusion capacity (37% vs 50%, $p = 0.039$). Older age and lower level of saturation were independently associated with higher mortality in COPD patients (OR = 1.096, 95% CI OR = 1.01-1.19, $p = 0.027$ and OR = 0.811, 95% CI OR = 0.68-0.96, $p = 0.015$, respectively).

Discussion

NLR and mortality

Chronic inflammation in COPD leads to the accumulation of neutrophils and lymphocytes and the production of inflammatory mediators. These mediators contribute to irreversible changes and tissue destruction, leading to a decline in lung function and diffusion capacity [18,19]. Consequently, markers associated with neutrophils and lymphocytes could be indicators of disease severity, prognosis, and outcomes. This study revealed that patients who died had higher NLR than those who survived.

Figure 1. Scatter plot for NLR and CRP.

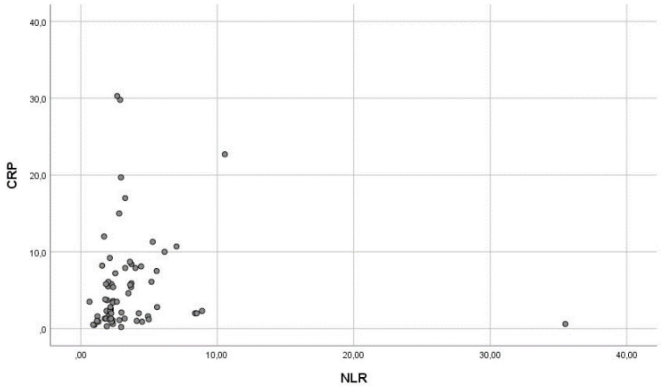
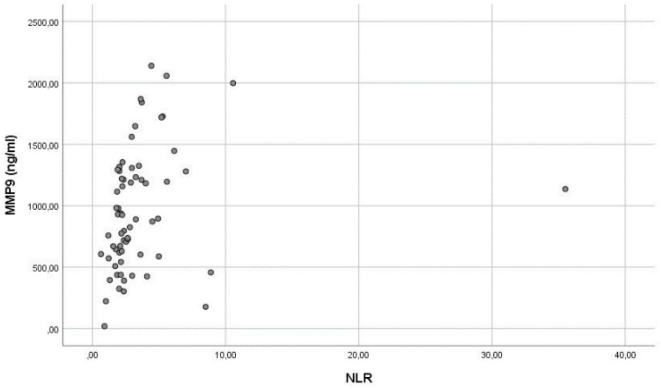


Figure 2. Scatter plot for NLR and MMP-9.



Xiong *et al.* suggested that elevated NLR could be associated with long-term mortality in COPD patients. They stratified 368 COPD patients into high and low NLR groups and found that the high NLR group had a higher exacerbation rate and a lower survival rate [20]. Similarly, Babaoğlu *et al.* found higher NLR values in deceased patients compared to discharged patients in their study [21]. Yao *et al.* also found that NLR and platelet-lymphocyte ratio (PLR) were significantly higher in AECOPD patients who died in the hospital than those who remained alive [22]. Paliogiannis *et al.* concluded that NLR is valuable in anticipating exacerbation and mortality in COPD patients [12]. Furthermore, Gayaf *et al.* demonstrated that higher age, elevated NLR, and lower mMRC values could predict 30-day and 90-day mortality [23]. Patients with higher NLR values should undergo closer monitoring for potential intensive care requirements. Overall, NLR serves a significant role in COPD as it can act as an indicator for hospitalization and can predict mortality, offering new insights into disease management and prognosis.

NLR and other inflammatory biomarkers

Continuous exposure to tobacco smoke causes oxidative stress and inflammation in the airways, leading to disbalance in protease activity, degradation of the extracellular matrix, gradual breakdown of alveolar structures, and remodeling of the airways. Around two-thirds of COPD patients exhibit at least one elevated serum inflammatory marker. Persistent elevation of these markers has been associated with disease progression, clinical and functional parameters, and the development of comorbidities. The most researched serum inflammatory markers include CRP, cytokines, MMP, and others. However, their application in routine clinical practice could be enhanced. In contrast, NLR offers a rapid, simple, and cost-effective alternative, as it is derived from routine complete blood count tests. Studies have investigated the role of NLR as a predictive biomarker in COPD. For example, Taylan *et al.* [8] evaluated NLR in 100 COPD patients. They retrospectively analyzed data from patients during acute exacerbation periods and repeated the measurements three months later during stable periods. Their findings revealed a significant correlation between NLR with CRP and White Blood Count (WBC in patients with COPD, both in AECOPD and stable disease. Bilir *et al.* [24] also investigated the role of NLR as an inflammatory biomarker in COPD. They included 467 COPD patients during stable periods and acute exacerbations (216 and 186 patients, respectively). They showed that NLR in COPD patients with exacerbations was significantly higher compared with the stable period and healthy controls ($p < 0.001$). The NLR was higher in COPD patients during the stable period than in healthy controls ($p < 0.001$). In that study they also compared NLR with other biomarkers and showed a strong correlation between NLR and CRP in stable-phase patients and those in the exacerbation group. Our findings reveal a positive association between NLR and CRP, MMP-9, TIMP-1, as well as the MMP-9/TIMP-1 ratio. This analysis highlights the potential of NLR as an inflammatory marker in COPD patients.

COPD, NLR, and comorbidities

In our study, over 50% of COPD patients had some form of cardiovascular comorbidity. However, when stratified according to NLR values as high and low groups, NLR values were not significantly higher in patients with COPD and CVD. Fabbri *et al.* (2007), introduced the concept of chronic systemic inflammation syndrome connecting COPD with other chronic comorbidities [25]. Sakurai *et al.* were the first to associate the link between the NLR ratio in patients with COPD and other comorbidities [26]. Still, they concluded that specific comorbidities in COPD patients do not influence NLR kinetics, as in our study. A study cohort of 140 COPD patients conducted by Yasar *et al.* showed that within the COPD group, those with metabolic syndrome showed significantly higher NLR levels than those without [27]. Additionally, the results from the study by Vaguliene *et al.* demonstrated a higher degree of NLR in lung cancer patients with or without COPD compared to COPD patients only or healthy individuals [28].

This study is limited due to the small size of the study population and the fact that blood samples were collected only once, which prevents substantiating long-term potential elevation.

Conclusions

NLR in COPD correlates with inflammation and protease/antiprotease balance, with elevated NLR detected in deceased patients. These findings suggest that NLR can be a helpful clinical marker in COPD.

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Conflict of interests

No conflict of interests is declared.

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