

The Importance of Neutrophil to Lymphocyte Ratio and Peripheral Blood Eosinophilia in Chronic Obstructive Pulmonary Disease Patients with Acute Exacerbation: Recent Studies

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Abstract

Chronic obstructive pulmonary disease (COPD) is a chronic, progressive respiratory disease and the third leading cause of respiratory disease mortality. The diagnosis of COPD is changed to acute exacerbation of COPD (AECOPD) when respiratory symptoms become worse, beyond normal day-to-day variations and severely enough that changes in medication are required. Both neutrophils to lymphocyte ratio (NLR) and peripheral blood eosinophilia (PBE) are rapid and relatively inexpensive tests that can be easily applied in the clinical practice for the diagnosis and treatment of AECOPD patients. Furthermore, current studies found that NLR and PBE had a higher accuracy rate than other traditional markers (Leukocyte count and C-reactive protein) for the diagnosis and management of AECOPD. Besides, recent studies determined that NLR and PBE can be used for prediction of future exacerbations in COPD patients. This review aims to explore the current knowledge about the significance of NLR and PBE in AECOPD patients.

Keywords

Chronic Obstructive Pulmonary Disease, Acute Exacerbation, Neutrophil to Lymphocytes Ratio, Peripheral Blood Eosinophilia

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease characterized by the presence of poorly reversible airflow limitation and

airway inflammation [1]. COPD becomes the leading cause of morbidity and mortality around the world, were global mortality which estimated three million of death annually [2].

COPD is a disease with various pathological changes in airways, lung parenchyma and pulmonary vasculature [3] yet; COPD is a multifactorial disease with complex pathophysiological mechanisms and different syndromes that can alter the accuracy of the diagnosis and the treatment of the disease [4].

An acute exacerbation is defined the acute worsening for the patient's baseline of dyspnoea, cough and sputum production which is the hallmark of the symptoms of the disease [5] and is associated an increase in inflammatory markers that results in the reduction of lung function tests [6]. Although the pulmonary function tests are the most common traditional criteria used to assess the severity of the clinical phenotypes and the disease progression, lung function tests alone are not usually enough to diagnose the exacerbations of COPD [7]. According to those challenges, such inflammatory markers become reasonable to assess the severity and treatment of the disease.

In pathophysiological mechanisms of acute exacerbation, there are numerous and various types of inflammatory cells that participate in the pathological entity of the disease [8]. The predominant inflammatory cells are neutrophils, lymphocytes, macrophages, and eosinophils. Those inflammatory cells recruit and destroy lung parenchyma, which results in the clinical features of COPD [9].

The neutrophil to lymphocytes ratio (NLR) is an indicator that can be easily calculated from the routine blood tests, also is a rapid and relatively inexpensive test that is readily applicable in the clinical practice. Recent studies emphasized this index had a strong relationship to the systemic inflammatory response in AECOPD and other chronic diseases such as gastrointestinal cancers, cardiovascular disease and chronic renal failure [10] [11] [12].

Regarding the ideas of the above findings, the NLR is considered an essential index for the detection of severe acute exacerbations in COPD patients, while the traditional tests are showing normal ranges [12]. Although acute exacerbations in COPD are predominantly associated by neutrophilic infiltration, also there are strong evidence shows that eosinophilic airway inflammation can cause acute exacerbation in COPD patients [13].

Similarly, Peripheral blood eosinophilia (PBE) is a simple diagnostic test derived from a routine blood examination, and it's a relatively inexpensive and widely available test that can be identified patients at risk or have an acute eosinophilic exacerbation [14]. This review aims to explore the current knowledge about the significance of neutrophil to lymphocytes ratio (NLR) and peripheral blood eosinophilia (PBE) in COPD patients with acute exacerbation.

2. Neutrophil to Lymphocyte Ratio and AECOPD

Regarding the disease severity and exacerbation, Furutate *et al.* [15] investigated the relationship between NLR and the Clinical state in stable COPD patients (Table 1). They enrolled 141 stable COPD patients with their clinical parameters, and

Table 1. Recent studies investigating the significance of NLR in COPD patients with acute exacerbations.

Studies related for NLR in AECOPD							
No.	First author	Published year	Study design	Patients enrolled	Mean age (Years)	Gender (Male %)	Main findings
1	Ryuko Furutate [15]	2015	RS	141	71.2	95.9	The NLR was significantly higher in AECOPD patients compared to stable patients ($P < 0.001$)
2	Mahsuk Taylan [12]	2015	RS	100	63.9	60.6	NLR, CRP, WBC and ESR had significant correlation with the regard of AECOPD patients ($P < 0.001$, $P < 0.001$, $P < 0.002$ and $P < 0.0035$) respectively.
3	Heock Lee [16]	2016	CS	885	70.9	91.4	The NLR become a significant predictor during AECOPD ($P < 0.041$).
4	Aida M. Yousef [17]	2017	PS	188	48.9	62.6	NLR is significantly higher in patients with AECOPD ($P < 0.001$) than in stable patients.
5	Fei Teng [18]	2018	RS	906	81.9	42.5	NLR were significantly higher for 28 days mortality rate in AECOPD (ROC $\geq 8.130\%$)
6	Emine Aksoy [19]	2018	RS	10,592	68	69	The median NLR values were significantly higher for patients admitted at OPD/Ward/ICU with neutrophilic and eosinophilic endotypes ($P < 0.001$ and $P = 0.0081$), respectively.

Abbreviations: AECOPD: Acute exacerbations of chronic obstructive pulmonary disease; CS: Cohort study; CRP; C-reactive protein; ESR: Erythrocyte sedimentation rate; ICU: Intensive care unit; NLR: Neutrophil to lymphocyte ratio; OPD: Outpatient department; PS: Prospective study; PBE: Peripheral blood eosinophilia; RS: Retrospective study.

49 acute exacerbated patients to evaluate the significant variations of NLR. The patients mean age was 71.2 years, and 97.1% were men. There is a significant correlation in NLR to the BODE index and pulmonary function tests ($P < 0.001$). Also, the Body Mass Index (BMI), 6-Minutes' Walk Distance (6-MWD), fat-free mass index (FFMI) and airflow obstruction had a significant correlation to NLR ($P < 0.001$, $P < 0.001$, $P = 0.001$ and $P < 0.001$, respectively) but not fat mass index (FMI) and Charles index. There is a significant association between NLR and the clinical parameters after adjusting for age, sex, Charles index, and the smoking status. However, those associations suggest that NLR becomes a viable predictor of acute exacerbations in COPD patients. Finally, the investigators presented that NLR is significantly higher to AECOPD patients compared to stable COPD ($P < 0.001$).

In another study, M. Taylan *et al.* [12] retrospectively enrolled 100 AECOPD

patients and 80 ex-smokers without COPD as a control group to assess the importance of NLR for identifying the severity of inflammation and recognition of acute exacerbation. The mean ages of AECOPD and control group were (64.2 ± 11.3 years and 63.5 ± 12.2 years) respectively. According to the Global initiative for chronic obstructive lung disease (GOLD) stages, 43 patients were stage III, 57 patients were stage IV. The NLR, WBC, CRP, and ESR were significantly higher in AECOPD patients compared to the control group. The mean NLR values of stable, AECOPD patients and control group were 3.1 ± 2.5 , 7.1 ± 5.4 and 1.7 ± 0.9 respectively. Comparing the mean NLR values of the three groups, the mean values of NLR in acutely exacerbated patients was significantly higher ($P < 0.001$). By using Pearson correlation analysis, a significant correlation was found for NLR with CRP, WBC and ESR ($r = 0.50415$, $P < 0.001$; $r = 0.50304$, $P = 0.002$ and $r = 0.50275$, $P = 0.035$) respectively. A cutoff value of 3.29, NLR had a significantly higher sensitivity (80.8%) and specificity (77.7%) in ROC curve analysis than the CRP, WBC, and ESR (AUC 0.894, $P = 0.001$). Thus, the NLR appears a potential indicator for acute exacerbation in COPD patients.

Heock *et al.* [16] recruited 885 patients with COPD from 44 referral hospitals in Korea for a cohort study to evaluate the relationship of the NLR with the disease severity of airflow obstruction and acute exacerbations in COPD patients. The investigators categorized all the enrolled patients into 4 quartiles ($Q1 < 1.43$, $1.43 < Q2 < 2.04$, $2.04 < Q3 \leq 2.94$, and $2.94 < Q4$) according to the NLR levels. The mean age of the patients was 70 ± 7.8 years, 91.4% was men.

As the NLR quartiles increased, the symptoms score and quality of life deterioration increased. The patients with higher NLR quartiles had a shorter 6-minutes' walk distance (6-MWD) ($P < 0.001$). There is a significant correlation for NLR and the severity of airflow limitation in lung function tests. In univariate logistic regression analysis, the NLR was significantly correlated with acute exacerbation frequency in the first year.

Aida *et al.* [17] prospectively enrolled 188 patients (60 stable COPD, 68 AECOPD and 60 control groups) to evaluate the predictive state and value of NLR as a new inflammatory marker of AECOPD patients, comparing to another well know inflammatory markers (CRP, ESR, and WBC). The mean NLR values of stable COPD, AECOPD and control groups were 2.36, 4.442, and 1.45 respectively, the mean NLR were significantly higher in AECOPD patients than those in stable and control COPD patients ($P < 0.000$). NLR, ESR, and CRP were also significantly higher in acutely exacerbated COPD patients compared to stable and control COPD patients. Regarding the receiver operating curve (ROC), the sensitivity and specificity of NLR was 86.7% and 76.7% respectively with a cutoff of 3.12 for the detection of acute exacerbation ($P < 0.001$). In Pearson correlation analysis showed a significant association of NLR with WBC, CRP and ESR ($P < 0.000$). Finally, the authors found that NLR inversely associated with the severity of airflow limitation, as measured by FEV1% predicted and absolute values ($P < 0.001$).

Fei *et al.* [18] investigated the role of NLR in the prediction of acute exacerbation.

tion in COPD patients. They conducted a retrospective study and enrolled 906 patients with AECOPD. The proportion for a male to female was 525 to 381, and the mean age was 81.86 ± 9.75 years old. During the study, 698 patients were successfully discharged from the hospital, 106 needed further medical treatment, and 38 cases died within 28 days. The NLR was significantly higher for patients were admitted before giving any treatment than after treatment (before discharge) according to Wilcoxon signed-Rank test ($P = 0.000$). 698 AECOPD improved after treatment and is divided into two groups (infected and non-infected), based on the need for antibiotic treatment. The infected group (664 cases), NLR were significantly higher before the treatment with antibiotics and then after treatment (7.05 ± 6.94 and 4.32 ± 5.21 respectively $P = 0.000$), where the WBC count showed a higher significant result before the treatment with antibiotic than after treatment (9.10 ± 4.23 and 6.71 ± 2.37 respectively $P = 0.000$). In non-infected group, the NLR and WBC were not significant different between the admission date (3.89 ± 2.02 and 6.72 ± 3.05) and the time for discharge (3.36 ± 2.11 and 6.16 ± 1.58) ($P = 0.052$ and $P = 0.304$). Besides, receiver operating characteristics (ROC) analysis the area under the receiver operating characteristic curve (AUC) is used to calculate the predictive value of NLR in 28-days of mortality rate, the ICU occupancy rate and the frequency needed for invasive mechanical ventilation in acutely exacerbated patients with COPD, the NLR had a higher AUC 0.737, 0.676 and 0.732 respectively. Applying 8.130 as the critical NLR to predict the 28-day mortality, the sensitivity and specificity was 60.5% and 74.8% respectively, also the significance of NLR to predict the frequency needed for invasive mechanical ventilation were calculated also ROC analysis, the sensitivity and specificity was 54.3% and 84.8% respectively by using the AUC 10.345.

A retrospective cross-sectional study conducted by Emine *et al.* [19] investigated the differences between NLR and other novel inflammatory markers according to the severity of acute exacerbation in COPD patients with both eosinophilic and neutrophilic endotypes. They enrolled 10,592 cases and collected the data of their laboratory tests (complete blood count “CBC”, C-reactive protein “CRP”, NLR, Platelet to lymphocyte ratio “PLR” and platelet to mean platelet volumes values). The majority of the cases were admitted at the outpatient department (7864), were the others admitted to the wards (2233) and ICU (495). During the study process, the cases were divided into eosinophilic and neutrophilic endotype groups according to their peripheral blood eosinophilia percentages ($\geq 2\%$ and $< 2\%$). The neutrophilic COPD patients (62%) had higher inflammatory markers compared with eosinophilic COPD patients (38%). Evaluating the mean NLR values of both COPD groups shows, that the mean NLR of neutrophilic endotypes were significantly higher than the eosinophilic endotypes 5.11 (2.92 - 9.64) and 2.62 (1.88 - 3.80) respectively ($P < 0.001$).

3. Peripheral Blood Eosinophilia and AECOPD

Hye *et al.* investigated the importance of inflammatory markers to AECOPD pa-

tients required to hospital admission. [20] They conducted a retrospective study enrolled 1688 COPD subjects admitted to the outpatient and the emergency departments (Table 2). According to their complete blood count, the patients were grouped into eosinophilic group (peripheral blood eosinophilia “PBE” > 2%) and neutrophilic group (Peripheral blood neutrophils “PBN” > 650 or leukocytes > 11.000/ml) and their clinical characteristics and treatment outcomes were compared. 605 patients were diagnosed and hospitalized as AECOPD (177 eosinophilia, 380 neutrophilic and 48 paucigranulocytic). The male ratio was lower, and the mean age was significantly higher in the neutrophilic group ($P < 0.001$), where the mean BMI was higher in the eosinophilic group ($P = 0.019$). The neutrophilic AECOPD cases had higher CRP levels ($P < 0.001$). Concerning lung function tests, the eosinophilic patients had higher FEV1 and FVC ($P < 0.001$ and $P = 0.009$, respectively) than the neutrophilic patients. Also, more additional regular drugs such as phosphodiesterase 4 inhibitors were prescribed in neutrophilic group than eosinophilic ($P = 0.026$), whereas in eosinophilic exacerbated patients, more corticosteroid medications ($P < 0.001$) and corticosteroid combined with antibiotics were used than in

Table 2. Recent studies investigating the significance of PBE in acute exacerbation patients with COPD.

Studies related for PBE in AECOPD							
No.	First author	Published year	Study design	Patients enrolled	Mean age (Years)	Gender (Male %)	Main findings
1	Hye Seon Kang [20]	2016	RS	605	69.89	85%	The eosinophilic exacerbations had better pulmonary function tests than non-eosinophilic patients with AECOPD ($P = 0.004$).
2	Zheng Qianglin [21]	2017	RS	559	NA	NA	AECOPD patients had a significantly high prevalence of eosinophilia than non-eosinophilic patients ($P < 0.001$).
3	Meltem Coban Agga [22]	2017	RS	1490	66	69	The non-eosinophilic patients with EACOPD had higher of NLR, WBC count and Neutrophil percentage count than in eosinophilic patients ($P < 0.001$, $P < 0.001$ and $P < 0.001$) respectively.
4	Robert S. Zeiger [23]	2017	RS	7245	71.3	57.1%	Patients with greater levels of eosinophilic counts were related to higher frequency of acute exacerbations, increased emergency department visits and hospitalizations (95% CIs, $P < 0.001$).

Abbreviations: RS: Retrospective study; AECOPD: Acute exacerbations of chronic obstructive pulmonary disease; NLR: Neutrophil to lymphocyte ratio; PBE: Peripheral blood eosinophilia.

neutrophilic AECOPD cases ($P < 0.001$). The duration of hospital stay was not significantly differed in both two groups, but percentages of patients admitted in intensive care unit (ICU) and those required mechanical ventilation (MV) were higher in the neutrophilic patients ($P = 0.004$ and $P = 0.005$, respectively). In mortality rate, both total and early mortalities were significantly higher in neutrophilic patients than in eosinophilic patients (1.1% vs 4.5%, $P = 0.043$ and 0.0% vs 2.9, $P = 0.022$, respectively).

Zeng *et al.* [21] conducted a retrospective study focusing on the prevalence of blood eosinophilia and clinical characteristics of AECOPD patients. The investigators recruited 559 AECOPD patients and divided them into two based on the levels of PBE count $\geq 2\%$ or $\geq 3\%$ on admission.

The prevalence of PBE $\geq 2\%$ patients and $\geq 3\%$ patients was 43.1% (241 patients) and 27.2% (152 patients) respectively. As to the other laboratory tests, leukocytes, neutrophils and monocytes count, and CRP levels were lower in $\geq 2\%$ eosinophilic patients ($P < 0.01$), while higher levels of basophils and lymphocytes counts were found in PBE $\geq 2\%$ patients ($P < 0.01$).

Finally, the researchers determined that COPD patients with acute exacerbation had a relatively high prevalence of eosinophilia counts, while basophil in eosinophilic patients is higher than non-eosinophilic patients with AECOPD ($P < 0.001$).

Regarding frequency in hospital admissions and re-admissions, the Ağca *et al.* [22] conducted an observational cohort study by assessing the association between PBE and NLR with the hospital admissions and re-admissions for AECOPD. They enrolled 1490 patients with AECOPD and divided them into two groups according to their peripheral blood eosinophilia (group 1, the eosinophilic group, PBE $> 2\%$; group 2, the non-eosinophilic group, PBE $\leq 2\%$). 633 patients were in group 1 and 857 patients were in group 2. Both groups were male predominant, and the mean ages were 66 ± 11 and 69 ± 11 years old respectively. The eosinophilic group had higher lymphocytes and eosinophilic percentages and hemoglobin level ($P < 0.001$), while the non-eosinophilic group had substantially higher leukocyte count and neutrophil percentages ($P < 0.001$). The mean NLR in the non-eosinophilic group was significantly higher (>5) than the eosinophilic group (<3). 66% (990) AECOPD patients were re-admitted to the hospital in the first 28 days in both groups, and the percentage of hospital readmission rate in each group was 60% and 40%, non-eosinophilic and eosinophilic groups respectively. Besides, 51% of non-eosinophilic cases were re-admitted, and 12% of eosinophilic cases were readmitted to hospital; also, the percentage of cases admitted to intensive care unit (ICU) was significantly higher in the non-eosinophilic group than in the eosinophilic group (3.0% and 1.7% respectively).

The relationship between peripheral blood eosinophilic count and COPD exacerbation were retrospectively investigated by R. S. Zeiger *et al.* [23]. A total of 7245 cases with AECOPD were enrolled, 57.1% of patients predominantly were men with white race (71.8%), and the percentage of current or ex-smokers were

(75.5%). The standard GOLD stage among the patients was 76.1%, and 25.4% were GOLD2 and 3, respectively. The exacerbation rate during the baseline of a year was 0.38 (95% CI, 0.37 - 0.40), 27% of patients exhibiting 1 or more and 7.0% had 2 or more COPD exacerbations, where 17.6% is having one or more COPD-related emergency ward visit or hospitalization. In results based on characteristics of eosinophilic count, the data were degraded into several strata according to the eosinophilic count and the percentages (PBE ≥ 50 cells/mm³ (80.3%), ≥ 150 cells/mm³ (47.8%), ≥ 300 cells/mm³ (19.0%), ≥ 400 cells/mm³ (10.2%) and ≥ 500 cells/mm³ (5.9%)). A comparison between the COPD group with ≥ 300 cells/mm³ (19.0%) and those with less than 300 cells/mm³ shows that males had significantly higher rates of acute exacerbations and COPD related admissions to emergency department or hospitalization, also had greater rates of short-term drugs prescribed (SABA and combinations of SABA/short-acting muscarinic agents or oral corticosteroids [OCs]), higher leukocyte, lymphocyte counts, and lower neutrophils count, but less co-morbidities of atrial fibrillation, anxiety, and depression. Indeed, the other COPD group with the lowest cut-off point (≥ 50 cells/mm³) significantly stated had more blacks, increased Charlson co-morbidity index score, and frequency of pneumonia, also a greater rate of COPD-related admissions in emergency departments or hospitalizations, higher levels of GOLD classification, and greater neutrophil counts. In according to the evaluation about the association between eosinophilic blood count and future COPD exacerbations, both univariate and multivariate analyses showed future COPD acute exacerbations, emergency department visits, and hospital admissions were frequently higher in COPD patients with greater eosinophilic counts.

4. Conclusion

Both peripheral blood eosinophilia (PBE) and neutrophil to lymphocyte ratio (NLR) are simple laboratory indexes that can be applied for the diagnosis and treatment of AECOPD cases. They have a higher accuracy rate than other traditional inflammatory markers such as leukocyte count and C-reactive protein. In addition, NLR and PBE may be applied for prediction of future exacerbation in COPD patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations List

6-MWD: 6-Minutes' Walk Distance;
AECOPD: Acute Exacerbations of Chronic Obstructive Pulmonary Disease;
AUC: Area under Receiver Operating Characteristic Curve;
BMI: Body Mass Index;
BODE index: Body Mass Index, Airflow Obstruction, Dyspnea and Exercise Capacity;
CBC: Complete Blood Count;
COPD: Chronic Obstructive Pulmonary Disease;
CRP: C-Reactive Protein;
CS: Cohort Study;
ESR: Erythrocyte Sedimentation Rate;
FEV₁: Forced Expiratory Volume in One Second;
FFMI: Fat-Free Mass Index;
FMI: Fat Mass Index;
FVC: Forced Vital Capacity;
GOLD: A Global Initiative for Chronic Obstructive Lung Disease;
ICU: Intensive Care Unit;
LABA: Long-Acting Beta-Agonists;
MV: Mechanical Ventilation;
NLR: Neutrophil to Lymphocyte Ratio;
OCSs: Oral Corticosteroids;
PBE: Peripheral Blood Eosinophilia;
PBN: Peripheral Blood Neutrophils;
PLR: Platelet to Lymphocyte Ratio;
PS: Prospective Study;
ROC: Receiver Operating Curve;
RS: Retrospective Study;
SABA: Short-Acting Beta-Agonists;
WBC: White Blood Cells.