

The role of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in exacerbation of chronic obstructive pulmonary disease

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Abstract

Objective: To investigate whether neutrophil-lymphocyte ratio and platelet-lymphocyte ratio like C-reactive protein can be used as markers of acute exacerbation in chronic obstructive pulmonary disease.

Methods: The cross-sectional study was conducted at Konya Training and Research Hospital, Konya, Turkey, between December 2012 and April 2013, and comprised patients with stable and acute chronic obstructive pulmonary disease. All participants were male and aged ≥ 40 years. Patients were included prospectively from outpatient and emergency units according to recent Initiative for Chronic Obstructive Lung Disease 2013 criteria. C-reactive protein, neutrophil-lymphocyte ratio and platelet-lymphocyte ratio of each group were measured and compared.

Results: Of the 94 patients, 48(51%) had stable disease with a mean age of 66.65 ± 10.17 years (range: 49-79 years), and 46(49%) had acute exacerbation with a mean age of 62.67 ± 9.41 years (range: 48-92 years). Mean levels of C-reactive protein, neutrophil-lymphocyte ratio and platelet-lymphocyte ratio were 5.04 ± 6.65 , 2.75 ± 1.11 and 137.39 ± 65.42 for stable disease, and 57.68 ± 58.49 , 7.99 ± 5.72 and 231.18 ± 141.36 for those with acute exacerbation ($p=0.001$). Cut-off values were neutrophil-lymphocyte ratio $=3.3$, platelet-lymphocyte ratio $=150$, and C-reactive protein $=5$ mg/dl. Positive predictive values for C-reactive protein, neutrophil-lymphocyte ratio and platelet-lymphocyte ratio were determined as 82% (odds ratio: 27.4); 85% (odds ratio: 32.5); and 73% (odds ratio: 6.3). Receiver-operating characteristic curve showed a significantly more area under curve of neutrophil-lymphocyte ratio (0.88) compared to platelet-lymphocyte ratio (0.74) ($p<0.05$).

Conclusion: During acute exacerbations of chronic obstructive pulmonary disease, neutrophil-lymphocyte ratio may be used as an easily measurable, available and cost-effective parameter with high prognostic accuracy in clinical practice.

Keywords: Chronic obstructive pulmonary disease, C-reactive protein, Neutrophil-lymphocyte ratio. (JPMA 65: 1283; 2015)

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterised by poorly reversible airflow limitation associated with an abnormal inflammatory response of lungs to noxious particles or gases, especially in people exposed to fumes and smoke.¹ Acute exacerbation of COPD (AECOPD), especially during infections, is among the most frequent reasons for hospitalisation. Approximately 4% of the general population in the western world is admitted with an acute respiratory disease at least once a year and nearly one-fifth of hospital visits is due to AECOPD.² Although the cause of exacerbations often remains unidentifiable, but up to 70% of exacerbations have recently been suggested to be infectious in origin with viruses as major triggers.³

AECOPD is defined as the deterioration in clinical picture with increased dyspnoea, a decrease in daily performance, an increase in sputum production, increased cough, and high fever.

Many studies show that there is an obvious increase in inflammation in airways during exacerbations among COPD patients who are generally categorised as mild, moderate and severe.^{4,5} The more severe the attack, the more is the inflammation present. If we consider an infection as the underlying COPD attack, we often base it on C-reactive protein (CRP) level in daily practice. Generally, the more severe the attack is, the higher is the level of CRP present in the haemogram.⁶

Recent studies have shown that neutrophil-lymphocyte ratio (NLR) can be used as a new inflammatory marker to assess the inflammation, particularly after such diseases as COPD and coronary artery disease (CAD).⁷ NLR is also found to be an inexpensive and feasible indicator in assessing the severity of malignant diseases in patients with an oncological history. Moreover, NLR was

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demonstrated as an independent predictor in certain specific clinical cases such as appendicitis like bacteriemia.^{8,9}

As infection, either bacterial or viral, is the main cause leading to clinical AECOPD, CRP is the common marker to show the existence of infection in patients with COPD. However, NLR and platelet-lymphocyte ratio (PLR) have not been used in the diagnosis of AECOPD. The present study was planned to determine whether NLR and PLR can be used like CRP in AECOPD diagnosis.

Patients and Methods

The cross-sectional study was conducted at Konya Training and Research Hospital, Konya, Turkey, between December 2012 and April 2013, and comprised patients with stable COPD (SCOPD) and AECOPD. All the subjects were male and aged ≥ 40 years who were enrolled prospectively from outpatient and emergency units according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2013 criteria; forced expiratory volume in 1 second (FEV1)/ forced vital capacity (FVC) <0.7 . GOLD divides patients into four subgroups as A, B, C, and D (ABCD).¹⁰ Patients were considered to have AECOPD if they met Anthonisen's criteria.¹¹ Patients with AECOPD were categorised according to the nature of expectoration either with mucoid or purulent sputum. Only SCOPD patients without a history of exacerbation for the last two months were recruited. Patients with a history of antibiotic treatment, use of systemic steroids with a prednisolone equivalent to >20 mg/day in the preceding two months, with disorders such as bronchiectasis (radiologically proven or history of phlegm expectoration >30 ml/day), tuberculosis or other inflammatory diseases such as malignancy, arthritis, inflammatory bowel diseases or connective tissue disorders, were excluded. Written informed consents were obtained from patients with both AECOPD and SCOPD.

Demographic features, results of pulmonary function tests and values of arterial blood gas analyses measured within 24 hours after the admission were obtained from AECOPD patient charts, whereas the results of SCOPD were recorded during clinical visits. FEV1, FVC and FEV1/FVC% were measured using a spirometer (Spirobank - MIR Medical International Research, Italy) according to the standards of the American Thoracic Society.¹² For arterial blood gas analyses, blood was drawn from the radial artery while the patients were breathing room air. Arterial oxygen and carbon dioxide tensions were analysed with a blood gas analyser [Radiometer ABL 800 Flex-Denmark]. An estimate of lifetime exposure to cigarette smoke (in pack-years) was

calculated as daily cigarette consumption (g) times duration of smoking (yr) divided by 20 (g/pack/years). Venous blood samples were drawn for leukocyte count (LC) and CRP, and analysed on the day of admission.

Peripheral venous blood samples were obtained using Ethylenediaminetetraacetic acid (EDTA)-containing blood collector tubes for CRP. The samples were centrifuged at 3000g for 5 min to separate plasma and stored at -80°C in deep freezer until performing CRP assays. CRP (Cardio Phase CRP, Siemens Healthcare Diagnostics Products GmbH, Hamburg, Germany) assays were performed by using whole-automated nephelometric assay device (BN II Siemens Healthcare Diagnostics Inc. Tarrytown, NY, USA).

For complete blood count (CBC), peripheral venous blood samples were obtained by using EDTA-containing blood collector tubes (BD Vacutainer EDTA, BD-Plymouth, UK), and CBC assays were performed by fully-automated device (ADVIA 2120 Hematology System, Siemens Healthcare Diagnostic Systems, Tarrytown, NY, USA).

To define NLR and PLR, CBC with automated differential counts, including neutrophils and lymphocytes, were made on admission. While the upper limit of neutrophil count for normal range was set at $8 \times 10^9/\text{l}$, the lower limit of lymphocyte count for the normal range was set at $0.9 \times 10^9/\text{l}$. NLR was calculated as the ratio of neutrophils to lymphocytes, both of which were obtained from the same automated blood samples for the study. PLR was calculated as the ratio of platelets to lymphocytes.

The study protocol was approved by the Ethics Committee of Selcuk Medical School of Selcuk University in Konya, Turkey. All statistical analyses were performed using SPSS 15. Descriptive analyses were performed for all variables. The association between two quantitative variables was evaluated using Pearson's correlation coefficient. The results were expressed as means and standard deviation for quantitative variables and as frequencies and percentages for categorical findings. To compare means of two independent groups, student's t test was used, while non-parametric data were analysed with Mann-Whitney U test. The Kruskal-Wallis test was used while non-parametric data of several groups were compared. To identify differences between the aforementioned markers, we performed an unadjusted and adjusted regression analyses, and a logistic regression analysis. Receiver operating characteristic (ROC) curves were constructed to evaluate the, specificity, positive predictive value (PPV) and negative predictive value (NPV) of CRP, NLR and PLR in predicting survival. ROC curves displayed such sensitivity versus 1-specificity that the area under the curve (AUC) was formed between 0.5

and 1.0 with higher values indicating increased discriminatory ability. The level of statistical significance was taken as $p < 0.05$.

Results

Of the 94 patients, 48(51%) had stable disease with a mean age of 66.65 ± 10.17 years (range: 49-79 years), and 46(49%) had acute exacerbation with a mean age of 62.67 ± 9.41 years (range: 48-92 years). Among the SCOPD patients, 16(33.3%) were in category B, and 18(37.5%) in category D. Among AECOPD patients, 34(73.9%) were in category D (Table-1).

According to their exacerbation intensity, 28(58.3%) SCOPD patients were in the mild category, while 31(67.4%) AECOPD patients were in the severe category.

FEV1 and partial oxygen pressure were found to be significantly lower in AECOPD (Table-2). Mean CRP levels were higher in patients with AECOPD compared to those with SCOPD ($p=0.001$) (Table-3). CRP measurements showed a sensitivity and specificity of 89.1% and 81.2%, respectively. PPV and NPV for CRP were 82% and 88%, and odds ratio (OR) and relative risk (RR) for CRP were 27.4 and

Table-1: New GOLD ABCD classification for exacerbated and stable COPD patients.

	SCOPD (n=48)	AECOPD (n=46)	
GOLD (A)	5 (%10.4)	1 (%2.2)	6 (%6.3)
GOLD (B)	16 (%33.3)	7 (%15.2)	23 (%24.4)
GOLD (C)	9 (%18.8)	4 (%8.7)	13 (%13.8)
GOLD (D)	18 (%37.5)	34 (%73.9)	52 (%55.3)
	48 (%100)	46 (%100)	94 (%100)

GOLD: Global Initiative for Chronic Obstructive Lung Disease

ABCD:

COPD: Chronic obstructive pulmonary disease

SCOPD: Stable chronic obstructive pulmonary disease

AECOPD: Acute exacerbation of chronic obstructive pulmonary disease.

Table-2: Analyses related to age, smoking history, PFT, ABG and BMI.

	SCOPD (n=48)	AECOPD (n=46)	p value
Age	62.67 ± 9.41	66.65 ± 10.17	0.05
Smoking history (Pack-years)	43.06 ± 34.61	40.09 ± 34.90	0.67
FEV1, % predicted	42.72 ± 13.81	35.65 ± 15.44	0.2
PaO ₂ , mmHg	64.92 ± 17.82	54.36 ± 11.57	0.001
PaCO ₂ , mmHg	38.56 ± 6.69	37.12 ± 7.86	0.34
BMI, kg/m ²	26.42 ± 4.32	25.42 ± 4.06	0.25

Figures are mean $\pm$ SD or numbers of subjects with percentages in parentheses. SCOPD: stable chronic obstructive pulmonary disease; AECOPD: acute exacerbation chronic obstructive pulmonary disease; PFT: pulmonary function tests; ABG: arterial blood gas; PaO₂: partial pressure of arterial oxygen; PaCO₂: partial pressure of arterial carbon dioxide; BMI: body mass index; FEV1= forced expiratory volume in 1 sec.; It was statistically significant ($p < 0.05$).

Table-3: Infection markers in patients with exacerbated and stable COPD on admission.

	SCOPD (n=48)	AECOPD (n=46)	p value
CRP (mg/l)	5.04 ± 6.65	57.68 ± 58.49	0.001
NLR	2.75 ± 1.11	7.99 ± 5.72	0.001
PLR	137.39 ± 65.42	231.18 ± 141.36	0.001

CRP: C-reactive protein, NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, SCOPD: stable chronic obstructive pulmonary disease, SCOPD: Stable chronic obstructive pulmonary diseases. AECOPD: acute exacerbation chronic obstructive pulmonary disease. It was statistically significant ($p < 0.05$).

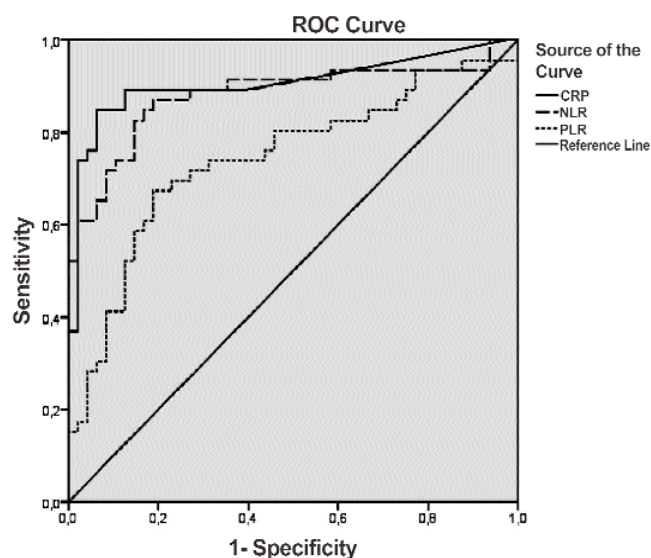


Figure: Comparison of receiver operating characteristic (ROC) curves between C-reactive protein, neutrophil-lymphocyte ratio and platelet-lymphocyte with respect to prediction.

6.8 respectively.

Mean NLR levels were significantly higher in AECOPD group compared to patients with SCOPD ($p=0.001$). NLR measurement demonstrated a sensitivity and specificity of 87% and 82%. PPV and NPV for NLR were 85% and 85%, and OR and RR were 32.5 and 5.8. A positive correlation was determined between NLR and CRP ($r=0.512$; $p < 0.001$).

Likewise, mean PLR levels were also significantly higher in AECOPD compared to SCOPD ($p=0.001$). PLR measurements had lower sensitivity and specificity of 74% and 69%. PPV and NPV were 73%, 70%, while OR was 6.3 and RR was 2.4. The correlation between CRP and PLR was lower than the correlation with NLR ($r=0.312$; $p < 0.001$).

AUC was 0.90 for CRP as a result of ROC curve. ROC for NLR showed AUC of 0.88, and this was better than AUC for PLR (0.74) (Figure). Accordingly, NLR was determined to be more sensitive and had higher rate in AECOPD patients like CRP as an indicator of inflammation compared to PLR.

Discussion

AECOPD is among the most common diseases in clinical practice, especially in patients with infections. The level of CRP, a marker of severity due to infections, was increased in AECOPD in accordance with several studies, compared to patients with SCOPD.^{13,14} As in our study, another study suggested CRP as a potential biomarker for the diagnosis of bacterial infections, especially in patients with AECOPD.¹⁵

One study has recently shown that CRP is the most selective biomarker among the 36 plasma biomarkers for confirming COPD exacerbation and predicting COPD severity.¹⁶ Although not sufficient for a definitive diagnosis per se, but CRP is concluded to be useful in confirming the diagnosis of exacerbation.

For many years, an easily measurable and noninvasive parameter which might reflect systemic inflammation has been researched. White blood cell (WBC), neutrophil counts, and CRP are still the most frequently used infection markers in daily clinical practice. Although infection markers such as procalcitonin, several cytokines, endothelin-1 and copeptin show promising results in the assessment of infection risk and in predicting outcome, the implementation of these relatively "new" markers is hampered by validation, cost, and accessibility factors.

In various stressful events, physiological response of circulating leucocytes is characterised by an increase in neutrophil counts and a decline in lymphocyte counts. Neutrophilia is caused by demargination of neutrophils, delayed apoptosis of neutrophils and stimulation of stem cells by growth factors. Margination of lymphocytes, re-distribution of lymphocytes and marked accelerated apoptosis are the supposed mechanisms of observed lymphocytopenia in infectious emergencies.¹⁷ Lymphocytopenia has shown promising results in the prediction of bacteremia in infectious emergency admissions.¹⁸

Recently, NLR has been "re-discovered" as a simple and promising marker in several clinical circumstances.^{19,20} Unlike many other inflammatory markers and bioassays, NLR is an inexpensive and readily available marker providing an additional advantage in predicting hospitalisation period and long-term mortality. A study

reported that NLR is a simpler marker in the determination of bacteraemia in emergency settings compared to CRP, neutrophil and WBC counts.⁹ In addition, NLR is relatively easy to assess without additional laborious efforts. In another study, NLR was reported to be highly sensitive in the determination of anticipated mortality in patients with community-acquired pneumonia.²¹ Consistent with our study, another study detected similar best cut-off value to NLR.²² In our study, NLR may be considered to be a sensitive marker like CRP to show the inflammation in AECOPD.

A recent study has shown a relationship between PLR and prognosis in colorectal cancer.²³ To our knowledge, the present study is the first to use PLR, like NLR, in determining inflammation in AECOPD.¹²

In a previous study, PLR was used as an independent factor in patients with ovarian cancer.²⁴ Another study evaluated both NLR and PLR in critical limb ischaemia and suggested that both NLR and PLR might be used in the analysis of survival.²⁵

The present investigation is one of the few studies further exploring the potential of such infection markers in patients with exacerbated and stable COPD. As NLR and PLR have been investigated little in AECOPD earlier, we planned to compare such valuable markers with CRP, a contemporary and commonly used marker. Although NLR and PLR levels were significantly higher in AECOPD patients, compared to SCOPD, we found NLR to be more sensitive than PLR. Furthermore, cut-off values determined in our study were consistent with those reported earlier; 3.2 for NLR and 160 for PLR.²⁵ Moreover, increased NLR was found to be positively correlated with CRP in patients with exacerbated COPD. According to ROC analyses, NLR showed an AUC which was higher than that for PLR, indicating it to be a more sensitive marker of inflammation in patients with AECOPD.

Conclusion

NLR, like CRP, both readily available and simple parameters, could also be used as a cost-effective marker of inflammation in AECOPD. However, more studies with higher patient series are required in order to highlight the role of NLR and PLR in AECOPD patients' response to the treatment and follow-up of exacerbations.

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