ORIGINAL ARTICLE

# Evaluation of the prognostic value of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in acute exacerbation of chronic obstructive pulmonary disease

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**Background:** The present study aimed at determining and comparing the prognostic value and the relationship of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios (PLRs) with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). **Materials and Methods:** The present case–control study was performed on 100 chronic obstructive pulmonary disease patients and 100 healthy subjects (controls). Age, gender, and laboratory results of complete blood count tests including lymphocyte count, neutrophil count, platelet count, hemoglobin level, neutrophil-to-lymphocyte ratio (NLR), PLR, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were obtained from the patient report and then recorded. The mentioned information was also completed for the control group. Following hospitalization, the patients that were discharged with clinically stable general status were re-examined, and the aforementioned laboratory information was rerecorded. **Results:** The results of the present study revealed that NLR with the sensitivity and specificity of 83.00% (74.2%–89.8%) and 93.00% (86.1%–97.1%) (cutoff value of 2.3), PLR with the sensitivity and specificity of 56.00% (46.0%–66.3%) and 83.00% (74.2%–89.8%) (cutoff value of 135.8), white blood cell (WBC) with the sensitivity and specificity of 69.00% (57.7%–77.8%) and 78.00% (68.6%–85.7%) (cutoff value of 8.5 × 103 µl), ESR with the sensitivity and specificity of 84.00% (75.3%–90.6%) and 99.00% (94.6%–100.0%) (cutoff value of 7.8), and CRP with the sensitivity and specificity of 52.00% (41.8%–62.1%) and 81.00% (71.9%–88.2%) (cutoff value of 1.9), respectively, had a significant prognostic value of AECOPD ($P < 0.001$). In addition to NLR had higher area under the curve (AUC) than PLR, WBC, and CRP. Therefore NLR had a better diagnostic value than the above three markers ($P < 0.001$). ESR also has higher AUC levels compared to PLR, WBC, and CRP and has a statistically better diagnostic value than them ($P < 0.001$), but did not differ significantly from ESR (difference between AUC: 0.02; $P = 0.059$). **Conclusion:** According to the results of the current study, NLR and PLR had a significant direct relationship with the two main markers of ESR and CRP, and both ratios had a significant prognostic value in AECOPD.

**Key words:** Blood platelets, chronic obstructive pulmonary disease, lymphocytes, neutrophils

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## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation symptoms, and its exacerbation is associated with a systemic inflammation in the airways.[1,2] The mentioned disease affects more than 200 million people worldwide, is the third leading cause of mortality in the world, and will be augmented in the coming years. COPD is typically associated with extrapulmonary manifestations such as systemic inflammation, cardiovascular disease, cancer, cachexia and muscle disorders, osteoporosis, anemia, depression, and anxiety.[3,4]

One prominent characteristic of COPD is acute exacerbation, which is generally associated with an increased inflammation due to environmental factors,

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or pure viral, pure bacterial, or combined viral and bacterial infections. Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is significantly associated with hospitalization, decreased quality of life, and increased rate of mortality. Therefore, a timely diagnosis of AECOPD seems indispensable to prevent the mentioned complications.[5]

Inflammation in COPD may play a role in many cell types such as macrophages, neutrophils, and lymphocytes.[6,7]

Neutrophils, as compared with macrophages, play a more crucial role in inflammation. Neutrophils, especially reactive oxygen species and neutrophil elastase, are main sources of proteases and are markers of acute inflammation.[8] In this regard, researchers have recently devoted due attention to the ratio of some inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) to evaluate their differentiation and the systematic inflammation in different types of diseases.[8-10] Compared with other inflammatory biomarkers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), these biomarkers are easy, fast, and cost-effective evaluations that can be performed using a simple complete blood count (CBC) test.

Recently, a number of studies have evaluated and compared the prognostic value and the predictive role of NLR and PLR with those of other inflammatory markers in the prognosis of AECOPD and reported conflicting findings in this respect. For instance, some studies have reported the acceptable predictive value of both NLR and PLR markers in AECOPD prognosis; however, the mentioned studies have proposed different cutoff values in this regard.[11-14] Some studies have considered these two markers in relation to other markers such as CRP and ESR.[11,15] In contrast, another array of studies has stated that the NLR marker may not be a good indicator for determining the disease severity in stable status of the disease; however, PLR can be considered as a good predicative marker for determining the disease severity in stable status of COPD.[16] Another study revealed that the accuracy of the NLR marker was higher than that of PLR and CRP, as a result of which recommendations have been put forward to use NLR in the treatment of patients.[13]

Hence, according to the presented literature review, few previous studies have evaluated inflammatory factors in the prognosis of AECOPD and have often paid attention to the prognosis of COPD. Furthermore, the evaluation of inflammatory factors in both acute and stable phases of the disease has not been considered in previous studies. In addition to the two factors of NLR and PLR, the evaluation of other inflammatory factors such as ESR, CRP, and white blood cell (WBC) can be valuable because a change in any of the inflammatory factors can have an effect on the other inflammatory factors. Given the lack of comprehensive studies in this respect, the present study conjectured that both NLR and PLR markers would be significant and worthwhile inflammatory markers that could detect the inflammatory status during AECOPD. Hence, the present study evaluated the relationship and prognostic value of these two markers in the acute exacerbation and stable statuses of COPD patients as compared with healthy subjects (controls).

## MATERIALS AND METHODS

### Study design and participants

The present study was a case–control study, the population of which was patients with AECOPD that were admitted to the emergency department of Al-Zahra Hospital in Isfahan in December 2018 to September 2019. According to the studies conducted in this regard[14] and considering the sensitivity of 86% yielded by NLR in the diagnosis of COPD, a 95% of confidence level, a power of 80%, an error of 0.1%, and a probability ratio of 0.5% for the incidence of COPD, 100 cases were selected. The sample was selected from patients with AECOPD as the case group and healthy individuals as the control group using the nonprobability convenience sampling technique.

One-hundred healthy individuals that were age-and gender-matched with the patients in the case group were selected as the control group from the nonsmokers without any risk factors or chronic diseases that accompanied the patients. Blood samples for CBC and inflammatory factors were also taken from the control group.

### Inclusion and exclusion criteria

The inclusion criteria for patients in the case group included the confirmed initial AECOPD diagnosis for the patient, confirmed prior COPD diagnosis for the patient by spirometry forced expiratory volume in 1 s to forced vital capacity (FEV1/FVC<0.70), and complete patient information (in case group).

In addition, the patient was excluded from the study and was replaced by a matched subject in case of the patients' dissatisfaction with participation in the study and use of their medical record information, incomplete patient medical record information, or diseases such as tuberculosis, severe structural lung diseases (such as bronchiectasis), cancer, any infectious or inflammatory diseases, other acute diseases accompanied with hospitalization (such as myocardial infarction, pulmonary embolism, and acute renal failure).

It should be noted that spirometry with ZAN GPI.3.00 (Germany) was performed in a spirometry laboratory

to diagnose COPD. If the ratio of postbronchodilator FEV1/FVC was <0.7, the Global Initiative for Chronic Obstructive Lung Disease guidelines was followed to diagnose COPD.[11]

The exacerbation of COPD was described if additional antibiotics or steroids were required and an acute deterioration of the respiratory symptoms beyond typical daily changes was observed in the patient.[12]

The absence of noteworthy variations in patient's symptoms in accompany with no additional need to doses of daily inhaler treatment or any further treatments was defined as stable COPD. The patients had stable COPD after 3 months.[11]

### Ethical committee approval and informed consent

This study was approved by the Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1397.276). Written informed consent was obtained from each of the subjects.

### Evaluation of inflammatory markers

The age and gender of the subjects as well as the laboratory results of CBC tests including lymphocyte count, neutrophil count, platelet count, hemoglobin level, NLR, PLR, CRP, and ESR were obtained from the patient report within 2 h of their admission to the hospital and then recorded. The mentioned tests were also performed for the control group, and the results were recorded.

Three months after the hospitalization, the patients that were discharged with clinically stable general status were re-examined, and the aforementioned laboratory information was rerecorded.

### Statistical analysis

Finally, the collected data were entered into Statistical Package for the Social Sciences (SPSS) (version 25; SPSS Inc., Chicago, Ill., USA). At descriptive statistics level, qualitative data were expressed as frequency (percentage), while the quantitative data were presented as either means standard deviation or medians (interquartile ranges). At the inferential statistics level, Chi-square test and an independent samples *t*-test were used to compare the frequency distribution of gender and the mean age between the two groups, respectively. According to the results of Kolmogorov–Smirnov test, the distribution of variables in this study was abnormal. Therefore, Mann–Whitney U test was used to compare the inflammatory markers between the two groups. Moreover, Wilcoxon test was used to compare these markers in the COPD in acute exacerbation and stable statuses. In addition, Spearman's correlation coefficient was used to examine the relationship of the inflammatory markers with each other. Then, a receiver operating characteristic (ROC) curve analysis was used to evaluate the areas under the ROC curve, which established the best cutoff values based on the Youden index for NLR, PLR, CRP, ESR, and WBC as the prognostic markers for AECOPD. Sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios were then calculated. Also MedCalc statistical software (version 19.3; MedCalc Software Ltd, Ostend, Belgium) was used to analyze and pairwise compare the diagnostic value of inflammatory markers from ROC analysis. In this comparison, using the DeLong *et al*. method, by determining the difference in area under the curve (AUC) level,[15] the differences ROC curves of inflammatory markers NLR, PLR, CRP, ESR, and WBC were investigated. The Significance level at 0.05 was considered in all analyses.

## RESULTS

The present study involved 100 healthy nonsmokers (control group), from whom 69% and 31% were male and female subjects, respectively with the mean age of 65.05 (10.51) years. Moreover, out of 100 AECOPD patients, 71% and 29% were male and female subjects, respectively, with the mean age of 67.80 (12.73) years. The patients in the case group had stable COPD after 3 months ($P > 0.05$). A comparison of demographic and laboratory data between the COPD and control groups is presented in Table 1.

Evaluation of the inflammatory markers revealed that the median values of WBC, ESR, CRP, NLR, and PLR were significantly lower in the control group as compared with the COPD group (in both acute exacerbation and stable statuses) ($P < 0.05$). In contrast, the number of platelets in the control group was significantly higher than that of the COPD group (in both acute exacerbation and stable statuses) ($P < 0.05$). In addition, NLR, ESR, and CRP levels decreased significantly following 3 months and shifting from AECOPD to stable COPD ($P < 0.05$) [Table 2].

In addition, the relationship of PLR with ESR and CRP in the control subjects ($r = 0.306$, $P = 0.002$; $r = 0.343$, $P < 0.001$, respectively), patients with AECOPD ($r = 0.572$, $P < 0.001$; $r = 0.536$, $P < 0.001$, respectively), and patients with stable COPD ($r = 0.253$, $P = 0.011$; $r = 0.357$, $P < 0.001$, respectively) was direct and significant; however, PLR indicated a weak and nonsignificant relationship with WBC ($P > 0.05$). Furthermore, the relationship of NLR with ESR and CRP in control subjects ($r = 0.642$, $P < 0.001$; $r = 0.682$, $P < 0.001$, respectively), patients with AECOPD ($r = 0.826$, $P < 0.001$; $r = 0.833$, $P <.01$). 0.001, respectively), and patients with stable COPD ($r = 0.764$, $P < 0.001$; $r = 0.691$, $P < 0.001$, respectively) was direct and significant. It should be noted that the relationship of NLR with WBC was also direct and significant in acute exacerbation and stable COPD

**Table 1: Demographic and laboratory data**

| Variables | Control (*n*=100) | COPD (*n*=100) | | *P* |
|---|---|---|---|---|
| | | Exacerbation | Stable | |
| Sex, *n* (%) | | | | |
| Male | 69 (69) | 71 (71) | 71 (71) | 0.758 |
| Female | 31 (31) | 29 (29) | 29 (29) | |
| Age (year) | 65.05 (10.51) | 67.80 (12.73) | 67.80 (12.73) | 0.097 |
| BMI (kg/m$^2$) | 31.32 (2.46) | 32.12 (2.60) | 31.98 (2.22) | 0.682 |
| Laboratory findings | | | | |
| Neutrophil (×10$^3$ µl) | 3.24 (2.18-5.53) | 6.32 (4.03-8.77) | 6.09 (4.21-8.91) | <0.001 |
| Lymphocyte (×10$^3$ µl) | 2.23 (1.35-3.43) | 1.38 (0.90-2.12) | 1.45 (0.94-2.20) | 0.092 |
| Hemoglobin (g/dl) | 13.25 (1.83) | 13.10 (1.62) | 14.53 (2.01) | 0.540 |

Data is shown as means (SD) or median (IQR). COPD=Chronic obstructive pulmonary disease; BMI=Body mass index; SD=Standard deviation; IQR=Interquartile range

**Table 2: Comparison of the inflammatory markers between healthy subjects and chronic obstructive pulmonary disease patients in stable and acute exacerbation statuses**

| Inflammatory markers | Median (IQR) | $P_1$ | $P_2$ | $P_3$ |
|---|---|---|---|---|
| WBC (×10$^3$ µl) | | | | |
| Control | 7.50 (5.32-8.50) | <0.001 | <0.001 | 0.362 |
| Exacerbation | 8.95 (6.42-11.27) | | | |
| Stable | 9.20 (6.75-11.80) | | | |
| Platelets (×10$^3$ µl) | | | | |
| Control | 239.50 (145.00-323.75) | 0.001 | 0.002 | 0.587 |
| Exacerbation | 177.50 (139.25-240.25) | | | |
| Stable | 192.50 (142.25-241.75) | | | |
| NLR | | | | |
| Control | 1.50 (1.30-1.80) | <0.001 | <0.001 | 0.038 |
| Exacerbation | 4.15 (2.82-8.17) | | | |
| Stable | 4.00 (2.30-6.67) | | | |
| PLR | | | | |
| Control | 102.05 (79.00-130.60) | 0.001 | 0.011 | 0.072 |
| Exacerbation | 129.05 (83.47-188.40) | | | |
| Stable | 114.65 (77.42-180.60) | | | |
| ESR | | | | |
| Control | 4.27 (2.84-5.21) | <0.001 | <0.001 | <0.001 |
| Exacerbation | 20.31 (11.74-25.32) | | | |
| Stable | 9.45 (7.35-11.50) | | | |
| CRP | | | | |
| Control | 1.00 (0.58-1.69) | <0.001 | <0.001 | <0.001 |
| Exacerbation | 5.58 (2.67-8.00) | | | |
| Stable | 2.00 (1.00-2.54) | | | |

$P_1$=Use of Man-Whitney test for comparison of control subjects versus acute exacerbation COPD patients; $P_2$=Use of Man-Whitney test for comparison of control subjects versus stable COPD patients; $P_3$=Use of Wilcoxon test for comparison of COPD patients with acute exacerbation status versus stable status. WBC=White blood cell count; ESR=Erythrocyte sedimentation rate; CRP=C-reactive protein; IQR=Inter quartile range; NLR=Neutrophil-to-lymphocyte ratio; PLR=Platelet-to-lymphocyte ratio; COPD=Chronic obstructive pulmonary disease

patients ($r = 0.333$, $P < 0.001$; $r = 0.362$, $P < 0.001$ respectively); however, the mentioned relationship was weak and insignificant in the control group ($P > 0.05$) [Table 3].

Finally, the prognostic value of inflammatory markers in AECOPD indicated that the cutoff value was 2.3 for NLR, which had the sensitivity (95% confidence interval [CI]) and specificity (95% CI) of 83.00% (74.2%–89.8%) and 93.00% (86.1%–97.1%) in AECOPD prognosis, respectively (AUC: 0.911, $P < 0.001$). Moreover, the cutoff value was 135.8 for PLR, which had the sensitivity (95% CI) and specificity (95% CI) of 56.00% (46.0%–66.3%) and 83.00% (74.2%–89.8%) in AECOPD prognosis, respectively (AUC: 0.639, $P = 0.001$). Furthermore, the cutoff value was 8.50 × 10$^3$ µl for WBC with the sensitivity (95% CI) and specificity (95% CI) of 69.00% (57.7%–77.8%) and 78.00% (68.6%–85.7%) in AECOPD prognosis, respectively (AUC: 0.668, $P < 0.001$). In addition, the cutoff value was 7.87 for ESR, which had the sensitivity (95% CI) and specificity (95% CI) of 84.00% (75.3%–90.6%) and 99.00% (94.6%–100.0%) in AECOPD prognosis, respectively (AUC: 0.931, $P < 0.001$). CRP also had a cutoff value of 1.90 with the sensitivity (95% CI) and specificity (95% CI) of 52.00% (41.8%–62.1%) and 81.00% (71.9%–88.2%) in AECOPD prognosis, respectively (AUC: 0.716, $P < 0.001$) [Table 4 and Figure 1].

Pairwise comparison of ROC curves of inflammatory markers showed that NLR had higher AUC than PLR, WBC and CRP and therefore had a better diagnostic value than the above three markers ($P < 0.001$). But did not differ significantly from ESR (Difference between AUC: 0.02; $P = 0.059$). ESR also has higher AUC levels compared to PLR, WBC and CRP and has a statistically better diagnostic value than them ($P < 0.001$) [Table 5].

## DISCUSSION

According to the results of this study, the number of WBCs as well as the ESR, CRP, NLR, and PLR levels in COPD patients (both stable and acute exacerbation statues) was significantly higher than that of the healthy subjects. In addition, with the change of disease status from AECOPD to stable COPD within 3 months, NLR, ESR, and CRP levels were significantly decreased ($P < 0.05$). Moreover, the relationship of PLR and NLR with CRP and ESR in AECOPD, stable COPD patients, and healthy subjects was significant and direct.

To clarify the mentioned finding, it can be stated that the exposure to a physiological stress can change the number of leukocytes so that the number of neutrophils and lymphocytes increases and decreases, respectively. Therefore, it is important to consider the use of these ratios as new inflammatory markers.[6,7,9]

In line with the present study, Yousef *et al*. indicated that the level of blood leukocytes, ESR, CRP, PLR, and NLR was higher and more constant in COPD patients as compared with healthy subjects.[14] In fact, many other studies, consistent with the findings of the present study, have shown the presence of inflammation even with lower levels in patients with stable COPD.[17,18]

Results of other studies have also indicated significantly higher levels of inflammatory markers in AECOPD patients as compared with stable COPD patients and healthy subjects.[19,20]

**Table 3: Relationship between the values of C-reactive protein, erythrocyte sedimentation rate, and white blood cell count with those of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in healthy subjects and chronic obstructive pulmonary disease patients with stable and acute exacerbation statues**

| Inflammatory markers | Control | | Exacerbation | | Stable | |
|---|---|---|---|---|---|---|
| | *r* | *P* | *r* | *P* | *r* | *P* |
| PLR | | | | | | |
| CRP | 0.306 | 0.002 | 0.572 | <0.001 | 0.253 | 0.011 |
| ESR | 0.343 | <0.001 | 0.563 | <0.001 | 0.357 | <0.001 |
| WBC | 0.095 | 0.349 | 0.090 | 0.375 | 0.070 | 0.487 |
| NLR | | | | | | |
| CRP | 0.642 | <0.001 | 0.826 | <0.001 | 0.764 | <0.001 |
| ESR | 0.682 | <0.001 | 0.833 | <0.001 | 0.691 | <0.001 |
| WBC | 0.021 | 0.834 | 0.333 | 0.001 | 0.362 | <0.001 |

*r*=Spearman correlation coefficient. WBC=White blood cell count; ESR=Erythrocyte sedimentation rate; CRP=C-reactive protein; NLR=Neutrophil-to-lymphocyte ratio; PLR=Platelet-to-lymphocyte ratio

Although the majority of these studies have evaluated markers such as ESR and CRP along with other inflammatory markers, the measurement of these markers is not feasible in clinical settings, especially in emergency departments. As a number of inflammatory markers such as PLR and NLR can be measured using routine CBC tests and yield similar results to those of ESR and CRP markers and all the mentioned four markers are directly associated with one another, the researchers of the present study have paid due attention to these markers.

In this regard, the results of the present study revealed that NLR with the cutoff value of 2.3 had the sensitivity of 83% and specificity of 93%, and PLR with the cutoff

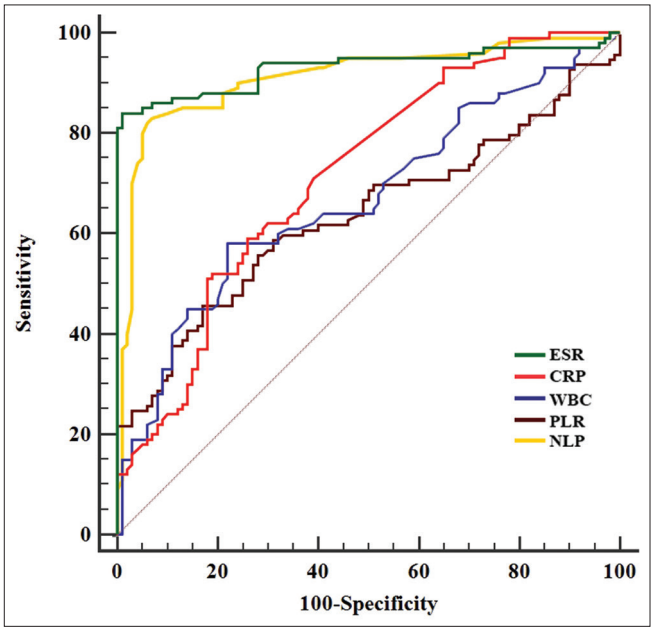


**Figure 1:** Receiver operating curve for neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, C-reactive protein, white blood cell, and erythrocyte sedimentation rate for acute exacerbation chronic obstructive pulmonary disease patients

**Table 4: Diagnostic value of inflammatory markers to identify acute exacerbation chronic obstructive pulmonary disease**

| Parameters of ROC | Inflammatory markers | | | | |
|---|---|---|---|---|---|
| | NLR | PLR | WBC (×10³ µl) | ESR | CRP |
| Youden index J | 0.760 | 0.290 | 0.360 | 0.830 | 0.330 |
| Cutoff | >2.30 | >135.80 | 8.50 | >7.87 | >1.90 |
| AUC (95% CI) | 0.911 (0.86-0.95) | 0.639 (0.57-0.70) | 0.668 (0.59-0.73) | 0.931 (0.88-0.96) | 0.716 (0.64-0.78) |
| *P* | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| Sensitivity (95% CI) | 83.00 (74.2-89.8) | 56.00 (46.0-66.3) | 69.00 (57.7-77.8) | 84.00 (75.3-90.6) | 52.00 (41.8-62.1) |
| Specificity (95% CI) | 93.00 (86.1-97.1) | 83.00 (74.2-89.8) | 78.00 (68.6-85.7) | 99.00 (94.6-100.0) | 81.00 (71.9-88.2) |
| PPV (95% CI) | 92.2 (84.6-96.8) | 73.0 (60.3-83.4) | 72.5 (61.4-81.9) | 98.8 (93.6-100.0) | 73.2 (61.4-83.1) |
| NPV (95% CI) | 84.5 (76.4-90.7) | 60.6 (51.9-68.8) | 65.0 (55.8-73.5) | 86.1 (78.4-91.8) | 62.8 (53.8-71.1) |
| +LR | 11.86 (5.8-24.4) | 2.71 (1.7-4.4) | 2.64 (1.8-4.0) | 84.00 (11.9-591.6) | 2.74 (1.8-4.3) |
| −LR | 0.18 (0.1-0.3) | 0.65 (0.5-0.8) | 0.54 (0.4-0.7) | 0.16 (0.1-0.3) | 0.59 (0.5-0.7) |

WBC=White blood cell count; ESR=Erythrocyte sedimentation rate; CRP=C-reactive protein; NLR=Neutrophil-to-lymphocyte ratio; PLR=Platelet-to-lymphocyte ratio; AUC=Area under the ROC curve; ROC=Receiver operating characteristic; CI=Confidence interval; PPV=Positive predictive value; NPV=Negative predictive value; +LR=Positive likelihood ratio; −LR=Negative likelihood ratio

**Table 5: Pairwise comparison of receiver operating characteristic curves**

| Inflammatory markers | Difference between AUC | SE[a] (95% CI) | *P* |
|---|---|---|---|
| NLR~PLR | 0.27 | 0.04 (0.19-0.35) | <0.001 |
| NLR~WBC | 0.24 | 0.04 (0.16-0.33) | <0.001 |
| NLR~ESR | 0.02 | 0.01 (0-0.04) | 0.059 |
| NLR~CRP | 0.19 | 0.25 (0.15-0.24) | <0.001 |
| PLR~WBC | 0.03 | 0.06 (−0.08-0.14) | 0.603 |
| PLR~ESR | 0.29 | 0.04 (0.22-0.37) | <0.001 |
| PLR~CRP | 0.08 | 0.04 (0–0.16) | 0.063 |
| WBC~ESR | 0.26 | 0.04 (0.18-0.34) | <0.001 |
| WBC~CRP | 0.05 | 0.04 (0-0.14) | 0.291 |
| ESR~CRP | 0.21 | 0.03 (0.16-0.27) | <0.001 |

[a]DeLong *et al*., 1988. WBC=White blood cell count; ESR=Erythrocyte sedimentation rate; CRP=C-reactive protein; NLR=Neutrophil-to-lymphocyte ratio; SE=Standard error; PLR=Platelet-to-lymphocyte ratio; AUC=Area under the ROC curve; ROC=Receiver operating characteristic; CI=Confidence interval

value of 135.8 had the sensitivity of 56% and specificity of 83% in the prognosis of AECOPD. In addition, other inflammatory markers including WBC, ESR, and CRP had acceptable and significant prognostic value in AECOPD. In addition, the findings revealed that WBC had the cutoff value of 8.50 × $10^3$ µl, the sensitivity of 69.00%, and the specificity of 78.00% in AECOPD prognosis. ESR had the cutoff value of 7.87, sensitivity of 84.00%, and specificity of 99.00% in AECOPD prognosis. Moreover, CRP had the cutoff value of 1.90, sensitivity of 52.00%, and specificity of 81.00% in AECOPD prognosis. In fact, in general terms, all the mentioned markers are appropriate and acceptable to be used in the AECOPD prognosis; however, the NLR and ESR markers had the highest area under the ROC curve.

Similarly, many previous studies have reported the suitability of ESR and CRP for the prediction of AECOPD;[15,21] however, some studies have stated that the mentioned two tests had a relatively low sensitivity and specificity in the diagnosis of the inflammation.[22] Moreover, some other studies have reported that sensitivity and specificity of ESR were higher than those of CRP, while others have identified CRP as an appropriate prediction marker for the inflammation.[23,24] In fact, it could be argued that these inconsistencies in the accuracy of these tests are due to the fact that the level of these markers can remain high for more than 3 weeks after the treatment, as a result of which they can show false positive values.[22]

In this regard, de Jager *et al*. revealed that lymphocytopenia (abnormally low level of lymphocytes in the blood) with the cutoff value of 1.0 × $10^9$/l, sensitivity of 73.9%, and specificity of 57.6% and NLR with the cutoff value of 10.0, sensitivity of 77.2%, and specificity of 63% are better predictors of bacteremia (blood bacteria) than normal parameters such as WBC, CRP, and neutrophil count in the intensive care units.[25]

Consistent with the findings of the present study, Yusef *et al*. showed that NLR with the cutoff value of 3.12 had the sensitivity of 86.7% and specificity of 76.7% in AECOPD prognosis and can be considered as the most sensitive marker in AECOPD diagnosis.[14]

In addition, Cockayne *et al*. revealed that the biological symptoms of neutrophil inflammation were directly and significantly associated with COPD severity. In fact, the mentioned finding can be related to the release of oxygen radicals and proteolytic enzymes such as neutrophil elastase and matrix metalloproteinases (proteases), which caused the tissue destruction of lung tissues.[19]

Karadeniz *et al*. also showed that PLR with the cutoff value of 152.2 had the sensitivity of 60% and specificity of 70%. The mentioned study suggested that PLR could be considered as a useful, available, and easy to administer test in comparison with other marker such as WBC, platelet count, mean platelet volume, and platelet distribution width to evaluate the ongoing inflammation and disease severity during stable and acute exacerbation statuses in COPD patients, respectively.[21]

In contrast with the findings of the present study, Hedhliabir *et al*. stated that NLR and PLR indicated a poor prognostic value and increased levels in AECOPD.[26] The results of the study conducted by Günay were in line with the findings of the current study. Günay's study has recognized NLR as a new inflammatory marker for the evaluation of the inflammation in COPD patients.[11] In addition, many other studies have evaluated the importance of NLR and PLR markers in the outcome prognosis of AECOPD patients and pointed to the significance of the prognostic value of these two markers. One study reported that PLR was more accurate in predicting the patient mortality 90 days after the discharge.[27] Furthermore, another study reported the NLR as a more accurate marker for the within-hospital mortality.[28]

Thus, although firm conclusions cannot be provided about the relative priority of the two mentioned ratios in the prognosis of AECOPD and researchers have evaluated this issue from different perspectives in different studies, it is definite that these two markers have a strong and significant relationship with AECOPD prognosis, COPD severity, and patient outcome. Therefore, it is recommended to conduct future studies evaluating these two markers along with other inflammatory markers in the prognosis of AECOPD or assessing the severity of COPD. Moreover, it is also suggested to monitor the patient outcome during the hospitalization and after the discharge and evaluate its association with the factors addressed in this study because in case of confirming the existence of this association, it

is possible to take an effective step in the management of patients outside the hospital by controlling inflammatory factors and applying the necessary treatment policies.

Therefore, given the limitations of the present study including the small sample size, the retrospective nature of the study, and the imprecision about the exact timing of blood sampling, which was attempted to be controlled by evaluating the inflammatory markers in the acute exacerbation and stable statuses of COPD, further and more comprehensive studies seem to be necessary in this field.

## CONCLUSION

According to the findings of previous studies, ESR and CRP are the two main markers in the evaluation and prognosis of AECOPD patients. However, recently, the role of other markers such as NLR and PLR has been discussed and attended to by researchers. Given the results of the present study, NLR and PLR had a direct and significant relationship with the two main markers of ESR and CRP, and both of these ratios had an acceptable and significant diagnostic value in the AECOPD prognosis. Hence, it seems that more attention can be paid to these two ratios in the prognosis of AECOPD.

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### Conflicts of interest
There are no conflicts of interest.

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