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Inflammatory Markers And Blood Gas Analysis In Determining The Severity Of Chronic Obstructive Pulmonary Disease

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Abstract

Aim: This study aimed to evaluate the severity of the disease using inflammatory markers in patients with Chronic Obstructive Pulmonary Disease (COPD) who admitted to the emergency department.

Materials and Methods: 193 COPD patients who applied to the emergency department were included in this retrospective study. Patients were divided into two groups according to the severity of COPD. The presence of type 1 and type 2 respiratory failure was used to create Group 2 (severe, very severe, life-threatening) and in the absence, Group 1 (mild, moderate). Inflammatory markers such as Neutrophil / lymphocyte ratio (NLR), Platelet / lymphocyte ratio (PLR), Lymphocyte / monocyte ratio (LMR) and disease severity were evaluated for both groups.

Results: The high COPD severity group (Group 2) had higher NLR and PLR values ($p < 0.001$, $p < 0.001$, respectively), and LMR values were lower ($p < 0.001$). There was infection in 46.2% of Group 2, while this rate was 13.5% in Group 1 ($p < 0.001$).

Conclusion: As the severity of the disease increases, NLR, PLR values increase, and LMR value decreases. This indicates that COPD attack will be severe in the presence of infection in COPD patients.

Keywords: Blood gas analysis; emergency medicine; inflammatory markers; chronic obstructive pulmonary disease (COPD)

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is defined as a permanent restriction of airflow and respiration in the airways and alveoli as a result of exposure to harmful particles and gases[1]. COPD is one of the leading diseases that cause serious morbidity and mortality in the world[2]. Along with increased admissions of COPD patients at the emergency department day by day[3], dyspnea, decrease in exercise capacity, sputum increase are the most common admission symptoms[4].

In addition, it is a progressive disease resulting from chronic irreversible peripheral alveolar and lung parenchyma caused by increased numbers of cells involved in the inflammatory response such as alveolar macrophage, neutrophil, T lymphocyte and release of proinflammatory cytokines[5]. Changes in hematological inflammatory markers of acute exacerbation COPD (AECOPD) cases have been shown to develop[6].

Neutrophil / lymphocyte ratio (NLR) was associated with lung functions, COPD acute attack and poor outcome[7], while Platelet / lymphocyte ratio (PLR) was found to be determinant for COPD acute exacerbation. Lymphocyte / monocyte ratio (LMR), on the other hand, is a new hematological inflammatory marker that has recently been detected in patients with pulmonary embolism, lung cancer, and coronary artery disease[8-10]. In addition, blood gas analysis is a valuable test used to evaluate COPD attack severity[11]. However, complete blood count (CBC) is an easily accessible, cheaper, and more widely used test[12].

Inflammatory processes in COPD are associated with severity of COPD attack. Also, the CBC test, which can be used just like blood gas in COPD attack but is more practical, provides a separate benefit in predicting the severity of COPD. In this study, it was aimed to evaluate the severity of disease using both known inflammatory markers such as NLR and PLR and new inflammatory markers such as LMR in COPD patients admitted to the emergency department.

Material and Methods

This retrospective study included 193 COPD patients over the age of 18 who applied to the emergency department between September 1, 2018 and August 31, 2019. Ethical approval was obtained from the local ethics committee of the University (Protocol: 2017-KAEK-189_2019.10.30_17). The authors adhered to the principles of the Helsinki Declaration during the study.

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Records of the patients (age, gender, clinical status, clinical course, blood samples, files and electronic records) who admitted to the emergency department and followed up with COPD according to ICD-10 codes (J44.0, J44.1, J44.8, J44.9) were evaluated. All data were used in analyzing of inflammatory hematological parameters (neutrophil/lymphocyte, platelet/lymphocyte, lymphocyte/monocyte ratio), C-reactive protein (CRP), attack severity and arterial blood gas values, if any.

COPD severity assessment even if there is no blood gas analysis in mild attack cases was evaluated as recommended by Burge et al.[13]. The patients were divided into two groups according to the severity of COPD. The presence of type 1 and type 2 respiratory failure was used to create Group 2 (severe, very severe, life-threatening) and in the absence, Group 1 (mild, moderate). For both groups, blood gas analysis, inflammatory markers and disease severity were evaluated according to the determined criteria. Furthermore, with or without any chest CT or Xray findings, with an increase in purulence of sputum, fever, increased white blood cell counts, with bacterial growth in sputum, secretions or BAL sample were taken, were accepted as the presence of infection.

Patients under 18 years of age who had congestive heart failure, chronic liver disease, diabetes mellitus, metabolic syndrome, deep vein thrombosis, rheumatic disease, inflammatory disease that may affect hematological inflammatory parameters were excluded from our study. In addition, patients who had deficiencies in electronic file records, detected laboratory errors, and inaccessible blood samples were not included in the study. However, patients who did not have blood gas parameters and who met the inclusion criteria were classified in group 1, but these 22 patients were not included in the analyzes performed according to blood gas.

Evaluation tools

Acute Exacerbation of COPD

Worsening of the patients' condition beyond normal day-to-day activity that required additional treatment with oral or intravenous corticosteroids or antibiotics; admission to an emergency for worsening of symptoms; a hospital admission with a new diagnosis of COPD.

Severity of COPD

In 2003, Burge et al. suggested that the severity of the disease can be assessed in 5 categories, regardless of whether patients with COPD had gas in the blood[13].

Mild: An exacerbation with antibiotics in the treatment but without systemic corticosteroids (assuming no respiratory failure if there is no blood gas).

Moderate: An exacerbation using systemic corticosteroids with or without antibiotics in treatment (assuming no respiratory failure if there is no blood gas).

Severe: Exacerbation (pO2 <60 mmHg, pCO2 <45 mmHg) with type 1 respiratory failure and hypoxemia, but without acidosis and carbondioxide retention.

Very Severe: Exacerbation with type 2 respiratory failure that can be compensated by hypoxia but with retention of carbondioxide without acidosis (pH>7.35, pO2 <60 mmHg, pCO2>45 mmHg, H + <44 nM).

Life-Threatening: The disease was classified according to criteria specified as exacerbation (pH <7.35, pCO2>45 mmHg, H + > 44 nM) with Type 2 respiratory failure accompanied by decompensated acidosis and carbon dioxide retention.

Laboratory Analyses

Hematological parameters were studied in tubes containing ethyleneditritrile-tetraacetic acid (EDTA) using the XN-1000 hematology analyzer (Sysmex Corporation, Kobe, Japan) within the first hour to prevent errors in the parameters. CRP was studied with serum gel tubes and Cobas 6000 analyzer (Roche Diagnostics, Mannheim, Germany). Blood gas samples were studied with Siemens Rapidlab 1265 blood gas analyzer (Siemens Healthcare Diagnostics, Medfield, MA, USA) within the first 10 minutes, protecting the cold chain with heparin injectors.

Statistical Analyses

Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS Inc; Chicago, IL, USA) version 20.0 software. The variables were determined using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to evaluate whether or not they are normally distributed. The independent sample t-test was used to compare continuous variables with normal distributions and the Mann-Whitney U test was used to compare variables with non-normal distributions. Analysis results of different variables were given as mean ± standard deviation, median (minimum-maximum), n (%) by investigating the test results. The Chi-square test or the Fischer's exact test (when the Chi-square test assumptions do not hold due to low expected cell counts), where appropriate, was used to compare the proportions in different groups. The relationship of inflammatory markers with COPD severity was evaluated with ROC analysis, and sensitivity and specificity of the values were calculated. A value of $p<0.05$ was accepted as statistically significant.

Table 1. Demographic data and clinical parameters of patients

Variables		group 1 (n=74)	group 2 (n=119)	p value
Age		69.01±10.66	73.20±12.44	0.017*
Gender, n (%)	male	36 (48.6)	74 (62.2)	0.647µ
	female	38 (51.4)	45 (37.8)	
Fever, n (%)	yes	6 (8.1)	34 (29.4)	<0.001µ
	no	68 (91.9)	85 (70.6)	
Infection, n (%)	yes	10 (13.5)	55 (46.2)	<0.001µ
	no	64 (86.5)	64 (53.8)	
Hospitalization, n (%)	yes	64 (86.5)	35 (29.4)	<0.001µ
	no	10 (13.5)	84 (70.6)	
Hospitalization time, median (min-max)		0 (0-9)	5 (0-30)	<0.001α

*: Student T test, α: Mann Whitney U test, µ: Chi-Square test
Data not normally distributed was shown as median (min-max.),
Normally distributed data was shown as mean ± standard deviation.

Results

Table 1 shows the comparison of demographic data and clinical parameters of patients with low attack severity (Group 1) and high attack severity (Group 2). The mean age of the patients with low attack severity (n = 74) was found to be 69.01 ± 10.66 years, and the mean age of the patients with severe attack (n = 119) was 73.20 ± 12.44 years. While 46.2% of the group with higher attack severity had infection, this rate was 13.5% in the group with lower attack severity (p <0.001).

Table 2 shows the evaluation of hematological and inflammatory markers of both groups. The group with higher COPD severity had higher NLR and PLR values (p <0.001, p <0.001, respectively), and LMR values were lower (p <0.001).

Blood gas analysis in both groups is shown in Table 3. While the pH, pO2 values of Group 2 were lower (p <0.001, p <0.001, respectively), PCO2, HCO3, H values were higher (p <0.001, p = 0.004, p = 0.002, respectively).

ROC analysis of inflammatory markers according to the severity of COPD disease is shown in Figure 1. In determining the severity of the disease, 4.33 cut off value had a sensitivity of 65% and a specificity of 66% for NLR.

While 94 (48.7%) COPD patients were hospitalized from the emergency department for clinical and intensive care, 99 (51.3%) COPD patients were discharged.

Discussion

According to the main findings of this retrospective study, the group with high COPD severity was found to have higher NLR, PLR values, and lower LMR values. At the same time, while 46.2% of the group with higher attack severity had infection, this rate was found to be 13.5% in the group with lower attack severity.

Table 2. Evaluation of hematological and inflammatory markers with the severity of COPD

Variables	Group 1 (n=74)	Group 2 (n=119)	p value
Wbc (103uL)	9.19 (2.85-20.89)	11.50 (4.62-31.48)	0.045α
Neutrophil (103uL)	5.94 (1.23-16.26)	7.76 (2.43-29.03)	0.001α
Lymphocyte (103uL)	1.80 (0.49-3.91)	1.42 (0.17-6.47)	<0.001α
Monocyte (103uL)	0.73 (0.11-2.14)	0.79 (0.05-1.80)	0.396α
PLT (103uL)	242.42±68.84	247.08±68.43	0.647µ
CRP (mg/dl)	7.55 (1-155.5)	26.10 (1-357)	<0.001α
NLR	3.60 (0.89-23.78)	5.36 (1.08-24.47)	<0.001α
PLR	132.73 (51.74-465.31)	169.40 (41.89-1638.89)	<0.001α
LMR	2.53 (0.61-9.78)	1.77 (0.32-7.27)	<0.001α

*: **Student T test**, α: **Mann Whitney U test**, µ: **Chi-Square test**
Wbc: White blood cell, PLT: platelet, CRP: C-reactive protein; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; LMR: lymphocyte to monocyte ratio
Data not normally distributed was shown as median (min-max.),
Normally distributed data was shown as mean ± standard deviation.

Table 3. Evaluation of the blood gas analysis with the severity of COPD

Variables	Group 1 (n=52)	group 2 (n=119)	p value
pH	7.40±0.43	7.37±0.78	<0.001*
pO2	55.50±19.54	39.82±12.30	<0.001*
pCO2	37.80 (23.00-66.50)	45.40 (24.80-105.60)	<0.001α
HCO3	24.35 (14.90-38.20)	25.80 (15.10-45.30)	0.004α
H	39.2 (29.76-47.33)	41.36 (28.91-85.51)	0.002α

*: **Student T test**, α: **Mann Whitney U test**
pH: Potential of Hydrogen, pO2: partial oxygen pressure, pCO2: partial carbon dioxide pressure, HCO3:bicarbonate, H: Hydrogen
Data not normally distributed was shown as median (min-max.),
Normally distributed data was shown as mean ± standard deviation.

Although there are various classifications for COPD, the most commonly used classification is the GOLD 2011. This classification is supported by symptoms, the severity of airflow limitation, history of exacerbation and presence of comorbidity[14]. Other known classification methods are BODE index (Body mass index, airflow Obstruction, Dyspnoea and Exercise), mBODE (BODE modified in grading of walked distance), ADO (Age, Dyspnoea, airflow Obstruction), DOSE (Dyspnoea, Obstruction, Smoking, Exacerbation)[15]. However, the classification made by Burge et al.[13] for the severity of disease of a patient who applied to the emergency department with an attack, seems to be more useful and practical because there is no blood gas requirement for COPD patients who apply with a light attack and no need for spirometry.

Potential of Hydrogen (pH), partial carbon dioxide pressure (pCO2), partial oxygen pressure (pO2) and bicarbonate (HCO3-) are parameters that show both the acid-base balance and respiratory functions of a person obtained as a result of blood gas test[16]. Arterial blood gas analysis is an indirect indicator of lung capacity and functions[17]. In various studies, it is known that venous blood gas, end-tidal carbon dioxide (ETCO2), pulse oximetry measurements were tried in COPD patients instead of using arterial blood gas. These studies show that there is an effort to use minimally invasive and non-invasive methods to determine the severity of the attack in COPD patients[18-20]. In a case with a severe AECOPD, pH and pO2 decreased, while PCO2 was expected to increase, pH significantly decreased, and PCO2 significantly increased. In the patient's intensive care follow-up, the need for non-invasive positive pressure ventilation (NIPPV), endotracheal intubation (ETI) was revealed[21].

In our study, in accordance with the literature, as the attack severity increased, blood pH, pO2 decreased and PCO2 increased. NLR is an inflammatory marker obtained by dividing the absolute neutrophil count by the absolute lymphocyte count. PLR is an inflammatory marker obtained by dividing the number of absolute platelets to the absolute number of lymphocytes[22]. It was reported that both markers, such as CRP and procalcitonin, showed an effective increase in inflammatory processes[23]. While Rovina et al.[24] determined the rate of NLR as 5.38 ± 4.6 in hospitalized patients with COPD attack, in our patients with high attack severity, this rate was found to be 5.36 (1.08-24.47). Demirtaş et al.[26] found the cut-off value for NLR was 9.39, with a sensitivity of 71.7% and a specificity of 61.1% in COPD attack patients. In our study, 4.33 cut off value had a sensitivity of 65% and a specificity of 66% for NLR according to the severity of COPD disease.

LMR is an inflammatory marker obtained by dividing the absolute lymphocyte count by the absolute monocyte count. Although it has been shown as a new prognostic biomarker that has been a precursor of the inflammatory response, like NLR and PLR, especially in cases of malignancy, unlike NLR and PLR, for example in stroke cases, its low value represents significance[9,25]. In a study, examining NLR, PLR, and LMR, although a relationship was found between NLR increase and death in COPD patients, it was reported that a similar relationship for PLR and LMR values was not found[27]. In our study, in the group with high attack severity, an increase in NLR and PLR and low LMR values were found significant. This shows that just like NLR and PLR, low LMR can be used as a predictor of severe COPD attack. In COPD patients, coexistence of infection is a very common condition[28].

In our study, the presence of infection is an indication of increased attack severity. Both the presence of infection and the cumulative effect of the attack results in an increase of inflammatory markers such as CRP, NLR and PLR, and reduction of LMR. Invasive and troublesome methods such as arterial blood gas and spirometry are used in the evaluation of COPD severity or during the diagnosis[29,30]. Furutate et al.[31] indicates that COPD severity can be predicted with some hematological inflammatory markers. In addition, although NLR and PLR are frequently used hematological markers[23], to the best of our knowledge, in the literature, LMR for COPD attack severity has not been studied.

Study Limitations

There are some limitations in our study. First, not having arterial blood gas analysis in all of our patients can be considered as a limitation, but it is also an advantage in terms of providing evaluation in patients with mild symptoms with-

out blood gas in the emergency practice. At the same time, because our study is a single-centered study, the limited number of patients is another limitation.

Conclusion

Although there are studies in the literature that previously examined the relationship between inflammatory markers and COPD disease, to the best of our knowledge, there is no two-way study that could evaluate the severity of the disease with inflammatory markers, with or without blood gas parameters. As the disease severity increases, the hospitalization rates increase and also NLR, PLR values increase. In addition, the newly used LMR value is decreasing. From another point of view, changes in inflammatory markers in COPD exacerbation cases directly affect disease severity and hospitalization rates. This shows that COPD attack will be severe in the presence of infection in COPD patients. The CBC test, which can be used just like blood gas in COPD attack but is more practical, provides a separate benefit in predicting the severity of COPD.

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