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Original Article

Can routine hemogram parameters be used as inflammatory biomarker in chronic obstructive pulmonary disease exacerbations?

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Abstract

Aim: Confirming the diagnosis and identifying the etiology are critical for the management of chronic obstructive pulmonary disease (COPD) exacerbation. There is limited use of hemogram and C-reactive protein (CRP) in distinguishing infectious or non-infectious in exacerbations. However, procalcitonin is more precious in making this distinction, although it is less accessible and more expensive. The aim of this study was to investigate the association between procalcitonin, CRP, hemogram parameters and ratios, and the efficacy of new hematological ratios in differential diagnosis in subjects with COPD exacerbation.

Materials and Methods: Subjects admitted to our outpatient clinic with the diagnosis of COPD were retrospectively analyzed and divided into 2 groups: those with acute exacerbation (n=52) and those are stable (n=64). Neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR) and platelet-lymphocyte ratio (PLR) were calculated for both groups. Subjects were grouped according to NLR cut-off point determined by the ROC curve (NLR <3.03 and NLR ≥ 3.03) and were compared in terms of variables.

Results: Comparing the values of NLR, PLR and MLR, all of these were significantly higher in the exacerbation group ($p < 0.001$). A positive correlation with WBC, neutrophil count, NLR, PLR, MLR, RDW, PDW and a negative correlation with lymphocyte count, PCT and MPV were detected in the correlation analyzes between exacerbation rate and hemogram parameters. When NLR ≥ 3.03 (n = 63) and NLR <3.03 (n = 53) groups were compared it was remarkable that exacerbation rate and procalcitonin were found significantly higher in group with high NLR ($p < 0.001$ and $p = 0.02$, respectively). However, there was no significant difference between two groups in terms of CRP values ($p = 0.32$).

Conclusion: This study has shown that basic hematological parameters routinely examined in clinical practice can be used like those of sophisticated biomarkers in acute exacerbations of COPD.

Keywords: Chronic obstructive pulmonary disease; exacerbation; neutrophil-lymphocyte ratio; procalcitonin

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of mortality and morbidity globally (1). COPD exacerbations may lead to an increase in the patient's daily respiratory symptoms and eventually drug changes (2). At COPD exacerbation, confirming the diagnosis and defining the etiology are very important for the management of the treatment. The most important factors in the etiology are viral upper respiratory tract infections and viral/bacterial infections of the tracheobronchial system (3). However, it has been reported that the etiological factor could not be detected in approximately 1/3 of the patients in the exacerbation (4). The decision to start antibiotherapy in COPD exacerbation is based on the increase in sputum purulence and the severity of the exacerbation. Complete blood cells (neutrophil, lymphocyte, monocyte, etc.), sedimentation, and C-reactive protein (CRP) are frequently used in treatment decision as a laboratory test. The utility of increased neutrophil or CRP for differentiating infectious or noninfectious in exacerbations is limited (5). Procalcitonin is more precious because it increases only in bacterial infections and does not increase in any viral infections (6,7). However, procalcitonin is less accessible and more expensive analysis than the hemogram and CRP. In recent years, hemogram sub-parameters and their ratio to each other have been represented as indicators of inflammation in the studies (8,9). In this retrospective study, we aimed to investigate the relation between procalcitonin, CRP, hematological parameters and ratios and the effectiveness of new hematological ratios in the differential diagnosis in subjects with COPD exacerbation.

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MATERIALS and METHODS

The medical files of 116 subjects who were admitted with the diagnosis of COPD at our hospital's outpatient clinic from March 2018 to June 2018 were retrospectively evaluated. Written patient consent were obtained. COPD exacerbation is defined according to Global Strategy for the Diagnosis, Management and Prevention of COPD (GOLD) 2017 (1) as the following: sustained deterioration of the patient's condition and respiratory symptoms. The stable group was determined as patients who had not experienced an exacerbation in the last 2 years or were not hospitalized due to COPD.

Fifty-two of 116 subjects were included in the acute exacerbation group and 64 were in the stable group. Subjects with diabetes mellitus, coronary artery disease, chronic renal failure, congestive heart failure, and subjects using systemic steroids recently were excluded from the study. Demographic features, COPD stages, hemogram parameters, CRP, and procalcitonin values of the subjects were recorded. The COPD stages of the subjects were determined according to GOLD 2017 (1). Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and monocyte-lymphocyte ratio (MLR) were calculated for both groups. NLR was obtained by dividing absolute neutrophil count by absolute lymphocyte count, PLR was obtained by dividing platelet count by absolute lymphocyte count, and MLR was obtained by dividing the absolute monocyte count by the absolute lymphocyte count.

Statistical Analysis

Statistical analysis was performed using the SPSS 20.0 (Statistical Package for Social Sciences for Windows, Inc., Chicago, Illinois, USA) program. $p<0.05$ was considered statistically significant. The compatibility of the variables used in the study to the normal distribution was examined by the Kolmogrov-Smirnov test. Continuous variables were expressed as mean ± SD or median (minimum-maximum), and categorical variables were expressed as numbers and percentages. Comparison of categorical parameters between groups was made using Chi-square and Fisher's Exact test, and for continuous variables comparison, Student-t and Mann-Whitney U test were used. The relationships between the variables were evaluated by Pearson and Spearman correlation analyses. Receiver Operating Characteristic (ROC) curve analysis was used to determine the cut-off points of NLR, PLR, and MLR which can distinguish stable COPD group from exacerbation one. Subjects were grouped according to NLR cut-off point determined by the ROC curve (NLR <3.03 and NLR ≥ 3.03) and were compared in terms of variables.

RESULTS

Of the 116 subjects enrolled in the study, 52 were acute exacerbated COPD and 64 were stable COPD. There was no statistically significant difference between two groups in terms of age and gender. There were more advanced stage subjects according to GOLD classification in the exacerbation group and it was statistically significant ($p=0.001$). When the hemogram parameters were compared; white blood cells (WBC), neutrophil, red cell distribution width (RDW), and platelet distribution width (PDW) values were found to be statistically significant high in the exacerbation group ($p <0.001$). However, lymphocyte count, plateletcrit (PCT) and mean platelet volume (MPV) were significantly lower in the exacerbation group ($p <0.001$). When the NLR, PLR, and MLR values were compared between exacerbated and stable groups, all these values were significantly higher in the exacerbation group ($p <0.001$) (Table 1).

Table 1. Comparison of demographic, clinic and hematologic parameters between exacerbation and stable groups

Variable	Exacerbation Group (n=52)	Stable Group (n=64)	p value
Male	39 (75%)	38 (59.4%)	
Female	13 (25%)	26 (40.6%)	0.16
Age (years)	67.6 ± 8	67.9 ± 8.2	0.88
GOLD			
A	-	5 (7.8%)	
B	27 (51.9%)	41 (64.1%)	0.001
C	16 (30.8%)	18 (28.1%)	
D	9 (17.3%)	-	
Hemoglobin (g/dL)	13.4 ± 1.93	13.4 ± 1.87	0.99
WBC ($x10^9$/L)	12 (3.1-26.1)	7.9 (4.8-10.3)	<0.001
Neutrophil ($x10^9$/L)	8.6 (0.7-53.1)	2.2 (0.8-3.9)	<0.001
Lymphocyte ($x10^9$/L)	1.06 (0.12-5.45)	2.2 (1.4-3.5)	<0.001
PCT (%)	0.19 (0.07-0.34)	0.23 (0.15-0.32)	<0.001
MPV (fL)	8.18 (5.93-13.3)	8.55 (7.3-10.2)	<0.001
PDW (%)	18.6 (16.3-24.4)	16.5 (15.7-18.1)	<0.001
RDW (%)	16.9 (13-25.5)	14.5 (12.4-19.5)	<0.001
NLR	8.57 (0.7-53.1)	2.2 (0.8-3.9)	<0.001
PLR	211.1 (33.4-1134.8)	114.6 (78.9-199.4)	<0.001
MLR	0.5 (0.03-2.73)	0.27 (0.14-0.43)	<0.001
CRP (mg/L)	9.72 (0.66-32.3)	-	-
Procalcitonin (ng/mL)	0.49 (0.01-25.7)	-	-

In correlation analysis between exacerbation rate and hemogram parameters, a positive correlation with WBC (r = 0.48, p <0.001), neutrophil (r = 0.64, p <0.001), NLR (r = 0.75, p <0.001), PLR (r = 0.53, p <0.001), MLR (r = 0.54, p<0.001), RDW (r = 0.44, p <0.001), PDW (r = 0.74, p <0.001), and a negative correlation with lymphocyte count (r=-0.61, p<0.001), PCT (r=-0.42, p<0.001) and MPV (r=-0.26, p=0.005) was detected (Table 2). Threshold values were determined for NLR, PLR and MLR by ROC analysis. The cut-off values for NLR, PLR and MLR were found 3.03 (sensitivity: 86.5%, specificity 85.9%, area under the curve (AUC): 0.934) (Figure 1), 147.1 (sensitivity: 73.1%, specificity: 73.4%, AUC: 0.805) (Figure 2) and 0.323 (sensitivity: 80.8%, specificity: 81.2%, AUC: 0.814) (Figure 3), respectively. All subjects were grouped by NLR < 3.03 (n = 63) and NLR ≥ 3.03 (n = 53). These two groups were compared in terms of exacerbation rate, CRP and procalcitonin values. It was remarkable that exacerbation rate and procalcitonin were found significantly higher in the NLR ≥ 3.03 group (p <0.001 and p = 0.02, respectively). However, there was no significant difference between two groups in terms of CRP values (p = 0.32) (Table 3).

Table 2. Correlation analysis between exacerbation rate and hemogram parameters

	r (correlation coefficient)	p value
WBC (x10^9/L)	0.48	<0.001
Neutrophil (x10^9/L)	0.64	<0.001
Lymphocyte (x10^9/L)	-0.61	<0.001
PCT (%)	-0.42	<0.001
MPV (fL)	-0.26	0.005
PDW (%)	0.74	<0.001
RDW (%)	0.44	<0.001
NLR	0.75	<0.001
PLR	0.53	<0.001
MLR	0.54	<0.001

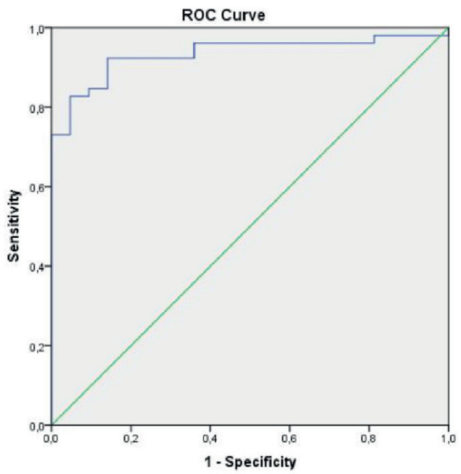

Figure 1. ROC curve for the determination of the cut-off for NLR and exacerbation in COPD. The cut-off level used in constructing this ROC is 3.03. The AUC for this relationship is 0.934 (sensitivity: 86.5%, specificity 85.9%)

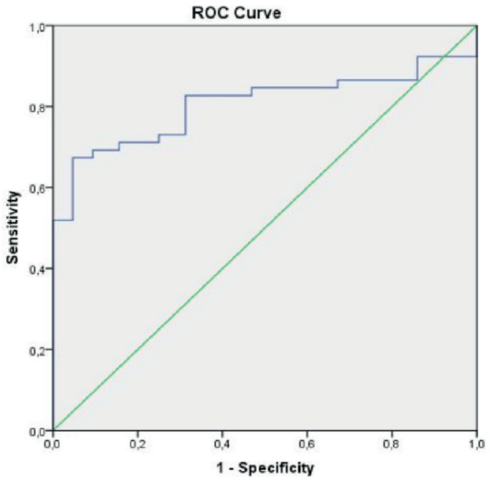

Figure 2. ROC curve for the determination of the cut-off for PLR and exacerbation in COPD. The cut-off level used in constructing this ROC is 147.1. The AUC for this relationship is 0.805 (sensitivity: 73.1%, specificity 73.4%)

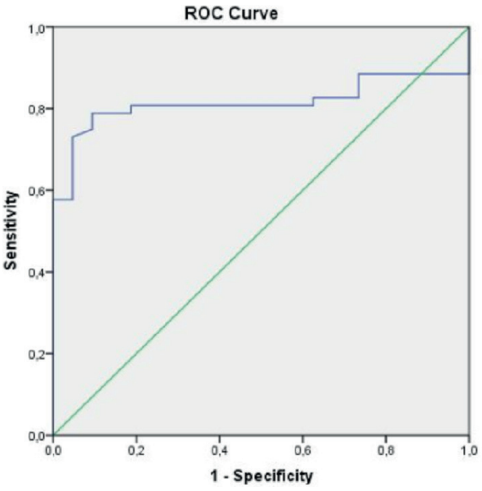

Figure 3. ROC curve for the determination of the cut-off for MLR and exacerbation in COPD. The cut-off level used in constructing this ROC is 0.323. The AUC for this relationship is 0.814 (sensitivity: 80.8%, specificity 81.2%)

Table 3. Comparison of exacerbation rate, CRP and procalcitonin levels between low and high NLR groups

	NLR<3.03 (n=63)	NLR≥3.03 (n=53)	p value
Exacerbation	8 (12.7%)	44 (83%)	<0.001
CRP (mg/L)	9.18 ± 6.74	12.05 ± 9.78	0.32
Procalcitonin (ng/mL)	0.25 ± 0.27	1.93 ± 4.58	0.02

DISCUSSION

Acute exacerbation is the most important reason of morbidity and mortality in COPD. Each exacerbation worsens the respiratory function and performance of the patients and increases the risk of recurrence of exacerbation. Patients applying with an acute exacerbation of COPD often have an underlying viral or bacterial infection. The distinction of whether the agent is bacterial or viral is very crucial for the management of treatment. Although the production of the specific agent

in culture is the most appropriate method for choosing the right antibiotic, in the meantime it can be late for the patients in acute exacerbation. Therefore, in daily practice, if the patient has three cardinal symptoms - an increase in sputum purulence, volume, and dyspnea - it is recommended to start antibiotics empirically before the sputum culture results. It is also recommended to start antibiotics, in case an increase at the amount and purulence of sputum, even no increase at dyspnea, and in severe attacks requiring ventilatory support (10). In patients applying with acute exacerbation, hemogram, CRP, and less frequently procalcitonin are routinely studied in the clinics. In this study, for COPD subjects applying with acute exacerbation, the relation between neutrophil, lymphocyte (which are sub-parameters of hemogram), NLR (which is obtained by dividing these by each other), CRP and procalcitonin, was investigated and also any hemogram parameter equivalent to procalcitonin was attempted to be determined.

The utility of CRP in bacterial infection in acute exacerbation of COPD was reported in many studies (11,12). Agusti et al. (13) showed CRP increased more in exacerbated COPD subjects with than stable subjects. On the other hand, in the same study, it was shown that CRP was significantly higher in subjects with stable COPD, compared to the control group. This suggests that CRP is a marker of inflammation rather than infection-specific.

Procalcitonin is a protein made of 116 amino acids and is considered to be calcitonin prohormone synthesized from the thyroid gland (14). Studies have shown that procalcitonin increases in only bacterial infections but does not rise in viral infections and other inflammatory conditions (6). In addition, in acute exacerbation of COPD, bacterial and viral infection could be differentiated by procalcitonin was reported in a few studies (15-18). However, considering the high cost and limited availability of procalcitonin, an alternative parameter that can be run cheaply and simply is needed.

When there is infection and inflammation in the body, there is an increase in neutrophils and a decrease in lymphocytes. The NLR obtained by dividing the absolute neutrophil count by absolute lymphocyte count was accepted as a parameter indicating both inflammation and physiological stress (19). Numerous studies have shown that NLR predicts the inflammation, long-term mortality at chronic subjects and is associated with disease severity (20-22). Several studies have reported that NLR can be used for early detection of COPD exacerbations and also as an indicator of exacerbation (23,24). Similarly, in our study, NLR has been found higher in the exacerbation group. In addition, in this study, also a positive correlation ($r = 0.75$, $p<0.001$) between the NLR and the risk of exacerbation was revealed when the correlation between the risk of exacerbation and hematological parameters was examined. In many studies, a relationship was shown between NLR and CRP, both were increased in COPD exacerbation when compared to stable subjects. Hereby, it is suggested that NLR can be used instead of CRP as an inflammatory marker in daily practice. Thus, it was stated that NLR can be used as an exacerbation marker and an inflammatory marker instead of other inflammatory markers, by using a simple hemogram survey and without the need for additional tests (22-27). Differently, in this study, also a correlation was revealed between NLR and procalcitonin. When the cut-off value for the NLR was determined as 3.03, in the higher NLR group, procalcitonin was also found significantly higher. Unlike, no statistically significant difference was detected for CRP between two groups of NLR according to the 3.03 cut-off value. This result suggested that NLR may be used as a marker of bacterial infection in COPD exacerbation, considering that procalcitonin is more specific for bacterial infections.

There are a few studies on the use of NLR in the differentiation between bacterial and non-bacterial infections in COPD exacerbations. However, at the end of all these studies, it has been suggested that NLR alone is not sufficient to differentiate bacterial and non-bacterial infection in COPD exacerbation and other inflammatory parameters should be used together with it (25,28,29). In COVID-19, a recent pandemic, NLR has been shown to be the severity marker of the disease (30). Whereas, there was no cut-off value determined in these studies. Perhaps, if a cut-off value had been specified, they could have made more precise recommendations for NLR, just like in our study. As a result, remarkably, our study supports NLR can be used alone as a distinction between bacterial-non-bacterial infection in COPD acute exacerbation by detection of procalcitonin and NLR correlation. In our study, PLR and MLR were also found to be high in the exacerbation group as well as NLR (Table 1), and a positive correlation was found between them and the risk of exacerbation. Accordingly, this study has shown that only NLR, among other hematological parameters, can indicate bacterial infection in acute exacerbations of COPD, such as procalcitonin.

CONCLUSION

This study demonstrated that hematological parameters routinely examined in clinical practice (especially NLR) can be used to predict bacterial infection like a biomarker (e.g. procalcitonin) in COPD acute exacerbations. Considering that procalcitonin is an expensive test, hematological parameters such as NLR may be preferred to detect bacterial infections.

Competing Interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical Approval: This study was approved by the Ataturk Pulmonary Diseases and Thoracic Surgery Training and Research Hospital's Education Board of Medical Specialties.

REFERENCES

1. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. Am J Respir Crit Care Med 2017;195:557-82.

2. Vogelmeier C, Hederer B, Glaab T, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. N Engl J Med 2011;364:1093-103.
3. Vestbo J, Hurd SS, Rodriguez-Roisin R. The 2011 revision of the global strategy for the diagnosis, management and prevention of COPD (GOLD)--why and what? Clin Respir J 2012;6:208-14.
4. Sykes A, Mallia P, Johnston SL. Diagnosis of pathogens in exacerbations of chronic obstructive pulmonary disease. Proc Am Thorac Soc 2007;4:642-6.
5. Vestbo J. Clinical assessment, staging, and epidemiology of chronic obstructive pulmonary disease exacerbations. Proc Am Thorac Soc 2006;3:252-6.
6. Wacker C, Prkno A, Brunkhorst FM, et al. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. Lancet Infect Dis 2013;13:426-35.
7. Karzai W, Oberhoffer M, Meier-Hellmann A, et al. Procalcitonin--a new indicator of the systemic response to severe infections. Infection 1997;25:329-34.
8. Lee SJ, Lee HR, Lee TW, et al. Usefulness of neutrophil to lymphocyte ratio in patients with chronic obstructive pulmonary disease: a prospective observational study. Korean J Intern Med 2016;31:891-8.
9. Kurtipek E, Bekci TT, Kesli R, et al. The role of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in exacerbation of chronic obstructive pulmonary disease. J Pak Med Assoc 2015;65:1283-7.
10. Anthonisen NR, Manfreda J, Warren CP, et al. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 1987;106:196-204.
11. Peng C, Tian C, Zhang Y, et al. C-reactive protein levels predict bacterial exacerbation in patients with chronic obstructive pulmonary disease. Am J Med Sci 2013;345:190-4.
12. Hurst JR, Donaldson GC, Perera WR, et al. Use of plasma biomarkers at exacerbation of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2006;174:867-74.
13. Agusti A, Edwards LD, Rennard SI, et al. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. PLoS One 2012;7:e37483.
14. Meisner M. Procalcitonin (PCT)-a new, innovative infection parameter. Biochemical and Clinical Aspects. 3. revised and expanded edition. New York: Thieme Stuttgart; 2000.
15. Chang C, Yao WZ, Chen YH, et al. [The changes and clinical implications of serum procalcitonin in acute exacerbations of chronic obstructive pulmonary disease]. Zhonghua Jie He He Hu Xi Za Zhi 2006;29:444-7.
16. Nseir S, Cavestri B, Di Pompeo C, et al. Factors predicting bacterial involvement in severe acute exacerbations of chronic obstructive pulmonary disease. Respiration 2008;76:253-60.
17. Zhang Y, Zhou L. [Diagnostic value of C-reactive protein and procalcitonin for bacterial infection in acute exacerbations of chronic obstructive pulmonary disease]. Zhong Nan Da Xue Xue Bao Yi Xue Ban 2014;39:939-43.
18. Ergan B, Sahin AA, Topeli A. Serum Procalcitonin as a Biomarker for the Prediction of Bacterial Exacerbation and Mortality in Severe COPD Exacerbations Requiring Mechanical Ventilation. Respiration 2016;91:316-24.
19. Gibson PH, Cuthbertson BH, Croal BL, et al. Usefulness of neutrophil/lymphocyte ratio as predictor of new-onset atrial fibrillation after coronary artery bypass grafting. Am J Cardiol 2010;105:186-91.
20. Nunez J, Nunez E, Bodi V, et al. Usefulness of the neutrophil to lymphocyte ratio in predicting long-term mortality in ST segment elevation myocardial infarction. Am J Cardiol 2008;101:747-52.
21. Sarraf KM, Belcher E, Raevsky E, et al. Neutrophil/lymphocyte ratio and its association with survival after complete resection in non-small cell lung cancer. J Thorac Cardiovasc Surg 2009;137:425-8.
22. Taylan M, Demir M, Kaya H, et al. Alterations of the neutrophil-lymphocyte ratio during the period of stable and acute exacerbation of chronic obstructive pulmonary disease patients. Clin Respir J 2017;11:311-7.
23. In E, Kuluozturk M, Oner O, et al. The Importance of Neutrophil-to-Lymphocyte Ratio in Chronic Obstructive Pulmonary Disease. Turk Thorac J 2016;17:41-6.
24. Bilir B, Altıntaş N, Aydın M, et al. The Predictive Role of Neutrophil to Lymphocyte ratio in Chronic Obstructive Pulmonary Disease. 2016;13.
25. Farah R, Ibrahim R, Nassar M, et al. The neutrophil/lymphocyte ratio is a better addition to C-reactive protein than CD64 index as a marker for infection in COPD. Panminerva Med 2017;59:203-9.
26. Furutate R, Ishii T, Motegi T, et al. The Neutrophil to Lymphocyte Ratio Is Related to Disease Severity and Exacerbation in Patients with Chronic Obstructive Pulmonary Disease. Intern Med 2016;55:223-9.
27. Yao C, Liu X, Tang Z. Prognostic role of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio for hospital mortality in patients with AECOPD. Int J Chron Obstruct Pulmon Dis 2017;12:2285-90.
28. van de Geijn GM, Denker S, Meuleman-van Waning V, et al. Evaluation of new laboratory tests to discriminate bacterial from nonbacterial chronic obstructive pulmonary disease exacerbations. Int J Lab Hematol 2016;38:616-28.
29. Tanriverdi H, Ornek T, Erboy F, et al. Comparison of diagnostic values of procalcitonin, C-reactive protein and blood neutrophil/lymphocyte ratio levels in predicting bacterial infection in hospitalized patients with acute exacerbations of COPD. Wien Klin Wochenschr 2015;127:756-63.
30. Lagunas-Rangel FA. Neutrophil-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. J Med Virol 2020.