ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Clinical Significance Of Neutrophil To Lymphocyte Ratio In The Assessment The Severity Of Chronic Obstructive Pulmonary Disease.

Zeinab H. El Sayed[1]*, and Zeinab Adawy[2].

[1]Department of Internal Medicine, Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt (MD).
[2]Chest Diseases Department, Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt (MD).

ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a debilitating condition characterized by permanent airflow limitation with pulmonary and systemic inflammation. Several studies reported that the neutrophil to lymphocyte ratio (NLR) in the peripheral blood was considered as a prognostic marker in several inflammatory diseases. Therefore, we aimed to evaluate the clinical significance of the NLR in the assessment of the severity COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline. 120 COPD patients conducted in this study were divided into four groups according to the GOLD severity of airflow limitation into mild (G-I), moderate (G-II), severe (G-III), and very severe (G-IV) groups. Complete blood counts (CBC), C Reactive protein (CRP) were measured and the NLR was calculated according to the neutrophil and lymphocyte counts from CBC. Spirometry was done at least three times for all patients. The severity of the symptom was determined by the Modified Medical Research Council breathlessness score. We used the COPD assessment test score to assess a patient's life. We found that the neutrophil count was gradually elevated from G-I to G-IV, in spite of the lymphocyte count which gradually decreased from G-I to G-IV. There was no significant difference in the total leucocytic count when compared it between the different groups. The maximum elevation of NLR was found in G-IV but the minimum was found in G-I. NLR was found to be significantly elevated in G-IV than G-III and significantly elevated in G-III than G-II, also, significantly elevated in G-II than G-I. NLR was inversely correlated with forced vital capacity (FVC) (r= -0.316, p= 0.000), forced expiratory volume in the 1 second (FEV1) (r= -0.390, p= 0.000) and FEV1/FVC(r= 0.234, p= 0.010). NLR was easily and cheap inflammatory marker which can be used as a follow-up inflammatory marker for COPD patient to assess the progression of COPD.

Keywords: Chronic Obstructive Pulmonary Disease; Neutrophil to Lymphocyte ratio; Neutrophil count; Lymphocyte count.

https://doi.org/10.33887/rjpbcs/2019.10.3.63

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a disease characterized by a progressive and permanent decline in pulmonary function, with a high rate of morbidity and mortality. The pathological hallmark of COPD is a chronic inflammation of the airways in response to inhalation of cigarette smoke and/ or polluted air. [1].

The measurement of pulmonary function is the most commonly accepted traditional markers to evaluate COPD severity. But, the pulmonary function test correlates poorly by the presence of specific symptoms and may not reliably reflect the severity of the pulmonary inflammatory state [2]. So, an additional easily measurable marker is needed to assess the severity of COPD and the treatment follow-up.

COPD is usually associated with persistent low-grade systemic inflammation at a stable stage and increased during exacerbation [3]. Indeed, the presence of this low-grade systemic inflammation is strongly affecting the quality of life and increase the mortality rate in COPD patients [2]. Systemic inflammation can be measured by using hematological and chemical biomarkers. Some of the systemic inflammatory biomarkers such as C-reactive protein, fibrinogen and leukocyte count are associated with impaired pulmonary function in patients with COPD [4].

Circulating neutrophil is well known as a systemic inflammatory marker. Moreover, previous studies reported that the neutrophil to lymphocyte ratio (NLR) in the peripheral blood is a reliable index of systemic inflammation, and can predict the severity and prognosis of many chronic inflammatory diseases [5] [6] [7]. Additionally, there are many authors found that NLR is increased in COPD patients when compared to healthy control [4]. However, the information about the NLR in COPD patients according to the severity of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline [8] was little. Therefore, we aimed to evaluate the clinical significance of the NLR in the assessment of the severity COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline.

Material and methods

Our cross-sectional study was conducted at Al- Zahraa University hospital, Cairo, Egypt, between March 2018 and December 2018. The current study was comprised of 120 COPD patients, who were admitted to Chest disease and Internal Medicine departments or from outpatient clinics. We excluded the COPD patients who had any condition that affected the neutrophil or lymphocyte count in the peripheral blood such as pneumonia, bronchiectasis, tuberculosis, malignancy or other inflammatory diseases. All patients had been receiving optimum medical treatment in the form of inhaled long-acting B2 stimulant, anticholinergic drugs, and an inhaled corticosteroid. Also, all patients do not receive oral or injectable corticosteroid in the last three months before conducting in our study. This study was done according to the ethical committee of the Faculty of Medicine, Al Azhar University, and was conducted in accordance with the Declaration of Helsinki. Informed consent was taken from all participants in this study. All patients underwent full medical history taking and full clinical examination.

The diagnosis of COPD patients were based on modified criteria by GOLD 2017 guideline [8]. All COPD patients had post-bronchodilator forced expiratory volume in the first second (FEV_1) less than 80% of the predicted value, and FEV_1/FVC (Forced vital capacity) not more than 70%. They had an increased FEV_1 less than 200ml or less than 12% of the baseline value, 15-20 minutes after puffs of inhaled salbutamol that was given via a metered-dose inhaler to differentiate between bronchial asthma and COPD.

The patients were classified according to the severity of airflow limitation based on Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline [8] into four groups, 30 patients included in each group:

GI: Mild group, their age ranged between 38 – 75 years ($FEV_1 \geq 80\%$).
GII: Moderate group, their age ranged between 25 – 67 years ($FEV_1 < 80$ to ≥ 50 %).
GIII: Sever group, their age ranged between 42 – 65 years ($FEV_1 < 50 \geq 30\%$).
GIV: Very sever group, their age ranged between 44 – 65 years ($FEV_1 < 30\%$).

All 120 COPD patients were subjected to the following: (all routine clinical tests were performed in the clinical pathology department and pulmonary function tests were done Respiratory department at Al Zahra hospital)

- Complete blood count.
- C Reactive protein.
- Erythrocyte sedimentation rate.
- Fasting and postprandial blood glucose level.
- Arterial blood gases.
- Plain X-ray chest.
- ECG.
- Transthoracic echocardiography.
- Pulmonary function tests:
    - ✓ Vital capacity (VC).
    - ✓ Forced expiratory volume in 1 s (FEV_1 %).
    - ✓ Forced vital capacity (FVC %).

The NLR was calculated by dividing the absolute count of a neutrophil by the absolute count of lymphocyte.

Resting ABG samples were taken while subjects in sitting position in ambient room air using blood gases analyzer Rapid Lab 248. The following parameters were recorded pH, arterial O_2 tension (PaO_2), arterial CO_2 tension ($PaCO_2$), and HCO_3

Complete blood count (CBC), C Reactive protein (CRP) and Erythrocyte sedimentation rate (ESR) were measured from peripheral venous blood samples of COPD patients at clinical pathology department in Al-Zhraa University hospital. The NLR was calculated according to the neutrophil and lymphocyte counts from CBC.

The lung function tests were carried out using Spirosift Spirometry 5000 FUKUD a NENSHI. Spirometric- indices were calculated using best of three technically satisfactory trials in accordance with the recommendation of American Thoracic Society [9]. The following parameters were recorded:

- FVC%
- FEV1%
- FEV_1/FVC%
- Peak expiratory flow rate
- FEF_{25-75}%

The severity of the symptom was determined by the Modified Medical Research Council breathlessness score (mMRC). We used the COPD assessment test (CAT) score to assess patient life.

Statistical analysis

Quantitative data were presented as the mean and standard error of the mean. The 95% confidence interval was calculated when suitable. ANOA was used to test the significance of the changes in the measured variables across time point.

Qualitative data were presented as number and percent. SPAA for Windows used in the interpretation of data. A p-value of 0.05 or less was considered statistically significant.

RESULTS

Table 1 shows the main characteristics of the study COPD patients. A total of 120 patients diagnosed with COPD were included in the current study. Based on GOLD guideline, patients were divided into four groups; G-I (mild), G-II (moderate), G-III (sever), and G-IV (very severe). The mean age of G-I patients was 50.20 ± 10.13 years, and 40% were current smokers. The mean age of G-II patients was 46.83 ± 11.94 years, and

73.3% were current smokers. The mean age of G-III patients was 58.27 ± 5.77years, and 73.3% were current smokers. The mean age of G-IV patients was 58.23 ± 5.22 years, and 63.3% were current smokers.

On the basis of mMRC dyspnea scale on G-I, we found 21 (70.0%) patients in mMRC grade 0, 8 (26.7%) patients in mMRC grade 1 and 1 (3.3%) patients in mMRC grade 2. While in G-II, there were 12 (40.0%) patients in mMRC grade 0, 11 (36.7%) patients in mMRC grade 1, 5 (16.7%) patients in mMRC grade 2 and 2 (6.7%) patients in mMRC grade 3. In G-III, we found 2 (6.7%) patients in mMRC grade 0, 2 (6.7%) patients in mMRC grade 1, 10 (33.3%) patients in mMRC grade 2 and 10 (33.3%) patients in mMRC grade 3, and 6 (20.0%) patients in mMRC grade 4. But in G-IV, there were 13 (43.3%) patients in mMRC grade 2, 11 (36.7%) patients in mMRC grade 3 and 6 (20.0%) patients in mMRC grade 4 as shown in table 1.

As regarding the neutrophil count

As shown in table 2, there was a significant increase of neutrophil count in G-II (3.97± 0.97) compared to G-I (2.93±0.53), (p = 0.000). When compared between G-III and G-IV, we found a significant increase in G-IV (6.66± 0.55) than G-III (4.63±0.66), (p = 0.000). Also, when compared between G-II (3.97± 0.97) and G-III (4.63±0.66), we found a significant increase in G-III than G-II, p-value = 0.001 as shown in table 2 and fig. 1.

As regarding the lymphocyte ratio

Table (2) also shows a significant elevation of mean± SD of lymphocyte in G-I (2.15± 0.69) in comparison to G-II (1.42±0.50), (P < 0.000). There was a significant increase of lymphocyte in G-III (1.57±0.45) in compared to G-IV (1.25± 0.08), (p = 0.000). But when compared between G-II (1.42±0.50) and G-III (1.57±0.45), we found no significant between them, (p = 0.171), (fig. 2).

As regarding the neutrophil to lymphocyte ratio

Table (2) also shows a significant elevation of mean± SD of neutrophil to lymphocyte ratio in G-II (2.75± 0.50) in comparison to G-I (1.55±0.53), (P < 0.000). There was a significant increase of neutrophil to lymphocyte ratio in G-IV (5.37±1.49) in compared to G-III (3.19±0.99), (p = 0.000). When compared between G-II and G-III, we found a significant increase in G-III (3.19±0.99) than G-II (2.75± 0.50), (p = 0.001), as shown in fig.3.

As regarding the White Blood Cell count

There was no significant difference of White Blood Cell count in G-I (6.96 ± 1.67) in compared to G-II (7.28 ± 2.07), (p = 0.512). When compared between G-III and G-IV, we found no significant difference in G-III (6.66± 0.55) than G-IV (4.63±0.66), (p = 0.206). Also, when compared between G-II (6.96 ± 1.67) and G-III (7.57 ± 1.56), we found no significant difference between them, p-value = 0.149 as shown in table 2 and fig. 4.

By Spearson's correlation study, there was no correlation between age and the neutrophil / lymphocyte ratio (r= 0.050, p= 0.585). Also, there was no correlation between Exp time and the neutrophil / lymphocyte ratio (r= 0.171, p= 0.062) as showmen in table 3.

Table (3) shows there was an inverse significant association between the neutrophil / lymphocyte ratio and vital capacity (r= 0.356, p= 0.000), and between FVC % (r= 0.316, p= 0.000). Also, there was an inverse significant correlation between the neutrophil / lymphocyte ratio and FEF_{25-75} % (r= 0.357, p= 0.000).

Table (3) also shows that there was an inverse significant association between the neutrophil/lymphocyte ratio and FEV_1/FVC % (r= 0.234, p= 0.010).

ISSN: 0975-8585

Table 1: Basic characteristics of the studied groups

Parameters		G I No= 30	G II No= 30	G III No= 30	G IV No= 30	P-value
Age/ years		50.20 ± 10.13 38 – 75	46.83 ± 11.94 25 – 67	58.27 ± 5.77 42 – 65	58.23 ± 5.22 44 – 65	0.000*
Sex	Male Female	23 (76.7%) 7 (23.3%)	24 (80.0%) 6 (20.0%)	24 (80.0%) 6 (20.0%)	27 (90.0%) 3 (10.0%)	0.572
Smoking status	Non smoker Smoker	18 (60.0%) 12 (40.0%)	8 (26.7%) 22 (73.3%)	8 (26.7%) 22 (73.3%)	11 (36.7%) 19 (63.3%)	0.023*
Diabetes Mellitus	No Yes	27 (90.0%) 3 (10.0%)	24 (80.0%) 6 (20.0%)	22 (73.3%) 8 (26.7%)	24 (80.0%) 6 (20.0%)	0.433
Systemic hypertension	No Yes	28 (93.3%) 2 (6.7%)	24 (80.0%) 6 (20.0%)	24 (80.0%) 6 (20.0%)	27 (90.0%) 3 (10.0%)	0.321
mMRC dyspnea scale: **0** **1** **2** **3** **4**		 21 (70.0%) 8 (26.7%) 1 (3.3%) 0 (0.0%) 0 (0.0%)	 12 (40.0%) 11 (36.7%) 5 (16.7%) 2 (6.7%) 0 (0.0%)	 2 (6.7%) 2 (6.7%) 10 (33.3%) 10 (33.3%) 6 (20.0%)	 0 (0.0%) 0 (0.0%) 13 (43.3%) 11 (36.7%) 6 (20.0%)	
CAT score	Median IQR)	1 (1 – 8)	4 (1 – 6)	20 (19 – 27)	23 (20 – 29)	0.000*
Blood gases: **Pco2** **Po2**	 Mean ± SD Mean ± S	 39.47 ± 2.76 84.34 ± 8.9	 39.61 ± 3.18 80.35 ± 7.22	 37.93 ± 6.24 70.5 ± 17.38	 48.82 ± 8.39 64.83 ± 7.65	 0.000* 0.000*
Pulmonary function : **VC ml** **FVC ml** **FEV_1 %** **FEV_1/FVC %** **FEF $_{25-75}$%**	 Mean ± SD Mean ± SD Mean ± SD Mean ± SD Mean ± SD	 96.93 ± 13.05 98.63 ± 17.82 93.37 ± 9.82 79.53 ± 10.75 73.3 ± 16.3	 69.6 ± 13.54 70.53 ± 13.79 61.3 ± 6.95 75.68 ± 13.17 54 ± 18.12	 57 ± 13.88 56.93 ± 15.5 40.2 ± 5.29 59.05±16.64 26.73±14.09	 42.73 ± 9.34 38.33 ± 10.6 23.23 ± 5.24 51.29 ± 6.53 12.77 ± 3.65	 0.000* 0.000* 0.000* 0.000* 0.000*

mMRC: Modified Medical Research Council; CAT: COPD Assessment Test; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; FEF $_{25-75}$%: Forced Expiratory Flow.

Table (2) The Comparative studies between groups as regarding Neutrophil, Lymphocyte, Neutrophil / Lymphocyte ratio, and White blood cells

Parameters		Mean± SD	P-value	Sig.
Neutrophil count (×109/L)	GI vs. GII	2.93±0.53 vs. 3.97± 0.97	0.000	S
	GIII vs. GIV	4.63±0.66 vs. 6.66± 0.55	0.000	S
	GII vs. GIII	3.97± 0.97 vs. 4.63±0.66	0.001	S
Lymphocyte count (×109/L)	GI vs. GII	2.15± 0.69 vs. 1.42±0.50	0.000	S
	GIII vs. GIV	1.57±0.45 vs. 1.25± 0.08	0.001	S
	GII vs. GIII	1.42±0.50 vs. 1.57±0.45	0.171	NS
Neutrophil to Lymphocyte ratio	GI vs. GII	1.55±0.53 vs. 2.75± 0.50	0.000	**S**
	GIII vs. GIV	3.19±0.99 vs. 5.37±1.49	0.000	S
	GII vs. GIII	2.75± 0.50 vs. 3.19±0.99	0.001	S
White Blood Cell	GI vs. GII	6.96 ± 1.67 vs. 7.28 ± 2.07	0.512	NS
	GIII vs. GIV	7.57 ± 1.56 vs. 8.36 ± 3.01	0.206	NS
	GII vs. GIII	6.96 ± 1.67 vs. 7.57 ± 1.56	0.149	NS

ISSN: 0975-8585

Table (3) Pearson's Correlation study between Neutrophil / Lymphocyte Ratio and other parameters

Parameters	Neutrophil / Lymphocyte Ratio		
	r	p-value	Sig.
Age	0.050	0.585	NS
VC	0.356*	0.000	S
FVC	0.316*	0.000	S
FEV_1 %	0.390*	0.000	S
FEF_{25-75} %	0.357*	0.000	S
FEV_1/FVC %	0.234*	0.010	S
Exp time	0.171	0.062	NS

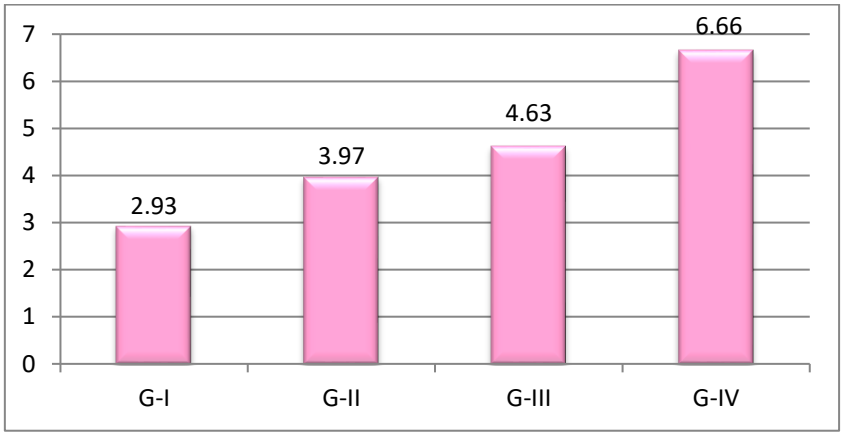

Fig. 1 represented the comparative study of neutrophil between groups

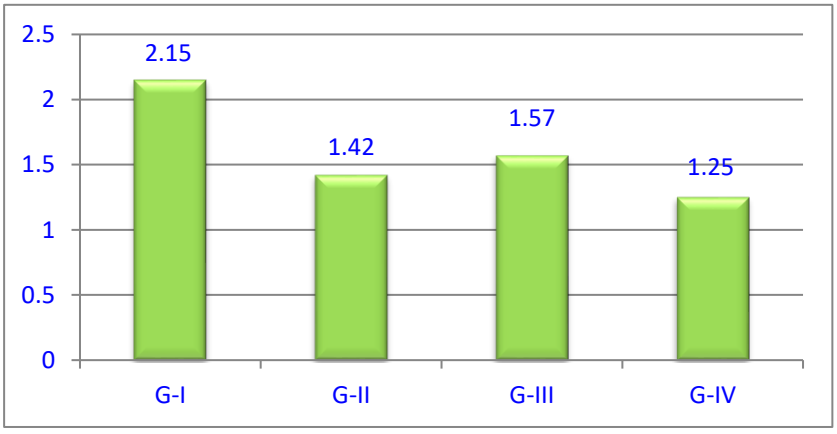

Fig. 2 represented the comparative study of lymphocyte between groups

ISSN: 0975-8585

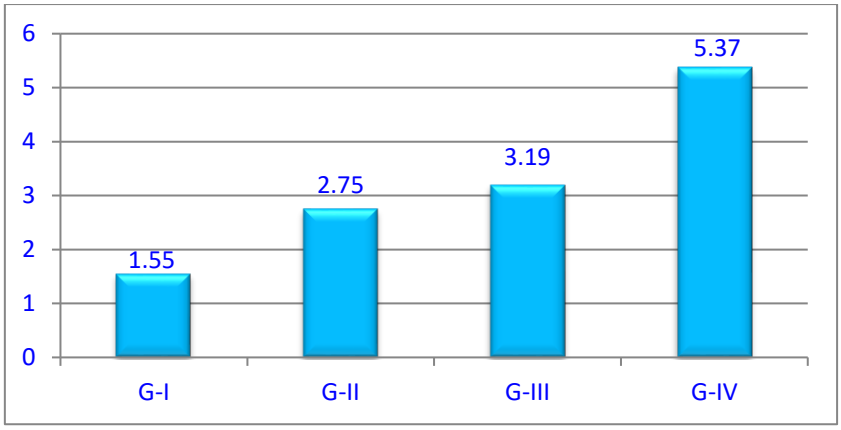

Fig. 3 represented the comparative study of neutrophil to lymphocyte ratio between groups

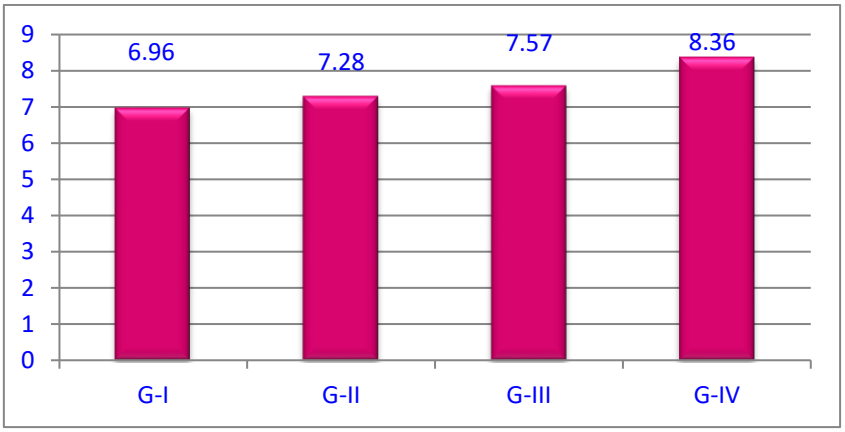

Fig. 4 represented the comparative study of total leucocytic count between groups

DISCUSSION

COPD is a debilitating condition characterized by progressive destruction of pulmonary tissue and the acute exacerbation is the commonest cause of death among them. It is accompanied by a low grade of systemic inflammation beside the pulmonary inflammation. There are many biomarkers have been studies in COPD to predict its severity but usually requires time for measuring [6]. Indeed, we need an easily measurable and non-invasive biomarker to reflect the COPD severity. Therefore, we aimed to evaluate the clinical significance of the NLR in the assessment of the severity COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline.

In our study, we demonstrated that there were significant differences in the mean of neutrophil to lymphocyte ratio between the studied four groups of COPD patients relative to the severity. When compared between mild and moderate groups, the mean of neutrophil to lymphocyte ratio was found to be significantly elevated in the moderate group than the mild group. Also, when compared to the mean of neutrophil to lymphocyte ratio between severe and very severe groups, we found a significant elevation in the very severe group than the severe group. Likewise, we found a significant elevation of the mean of neutrophil to lymphocyte ratio in the severe group when compared to the moderate group. Hence, our results suggested that the neutrophil to lymphocyte ratio was increased when the severity of COPD was progressed. A similar finding was reported by Yousef and Alkhiary study [10] who found that neutrophil to lymphocyte ratio was elevated with the severity of COPD. Aksoy et al. study [11] reported that the neutrophil to lymphocyte ratio can be used to predict the severity of exacerbation of COPD. Also, Rahimirad and his colleague [12] reported that the elevation of neutrophil to lymphocyte ratio was an independent prognostic biomarker for hospital mortality in acute exacerbation of COPD. A previous study also showed that the neutrophil to lymphocyte ratio increased with the severity of airflow obstruction and emphysematous change, suggesting that the neutrophil to lymphocyte ratio may reflect the extent of airflow obstruction [13] [14] [15]. Additionally, a recent study

reported that the elevated neutrophil to lymphocyte ratio was correlated with poor outcome [16]. Similarly, another study, as neutrophil to lymphocyte ratio increased, pulmonary airway narrowing increased. So neutrophil to lymphocyte ratio was considered as a predictive marker in expecting further COPD exacerbations [17].

In contrast, Günay et al. [4] and Lee et al. [18] reported that there was a significant difference of the neutrophil to lymphocyte ratio between the stable group of COPD and acute exacerbated of COPD group. But, there was a non- significant difference in relation to COPD severity in acute exacerbated COPD patients or in stable patients. Furthermore, other studies demonstrated that the neutrophil to lymphocyte ratio can predict the bacterial infection or the severity of community-acquired pneumonia in acute exacerbated COPD patients [19] [20] [21]. Also, a study was done by Van De Geijn et al. [22] found that the acute exacerbated COPD patients with bacterial infections had higher neutrophil to lymphocyte ratio values than those with non-bacterial infections.

In the present study, the circulating number of neutrophil was found to be gradually increased from mild group to very severe group, in contrast, the circulating number of lymphocyte was found to be gradually decreased from mild group to very severe group. Şahin et al [23] recognized a lower circulating lymphocyte count in COPD patients with acute exacerbated than those in a stable stage or healthy control and in lower also in stable COPD patients than in healthy control.

In our study, there was a significant inversely correlation between neutrophil to lymphocyte ratio and airflow limitation expressed by FEV_1, VC, FVC, and FEV1/FVC. Our result was similar to the finding of Lee et al. study [18] and Furutate et al. study [13] they found that the neutrophil to lymphocyte ratio was a significant inversely correlated with FEV1%. Also, Karatas et al. [24] showed the same result which found a negative correlation between neutrophil to lymphocyte ratio and FVC and FEV_1. Furthermore, another study reported that the circulating neutrophil count was inversely correlated with FEV1 % [25].

In contrast, a study found that the neutrophil to lymphocyte ratio was not correlated with FEV_1. However, there was a significant correlation between neutrophil to lymphocyte ratio and mMRC, and also between neutrophil to lymphocyte ratio and 6MWT [18]. Rhee et al. found the circulating neutrophil count was not correlated with FEV1% or the severity of asthma [26].

Based upon the results which stated previously, the neutrophil to lymphocyte ratio is superior to circulating neutrophil count alone or circulating lymphocyte count alone for the assessment of the severity of COPD [23].

CONCLUSION

The neutrophil to lymphocyte ratio can be used as a follow-up inflammatory marker for COPD patient to assess the progression and the severity of the disease. Notably, it is an easily done and cheap inflammatory marker.

REFERENCES

[1] Schmidt SA, Johansen MB, Olsen M, Xu X, Parker JM, Molfino NA, et al. The impact of exacerbation frequency on mortality following acute exacerbation of COPD: a registry-based cohort study. MJ Open. 2014;4: 12 e006729.

[2] Taylan M, Demir M, Kaya H, Selimoglu Sen H, Abaky O, Carkanat A, 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: 311-317.

[3] Suiss S, Dwll' Anillo, Ernst P. Long-term natural history of chronic of chronic obstructive pulmonary disease: severe exacerbation and mortality. Thorax.2012; 67:957-963.

[4] Günary E, Sarinc Ulasl S, Akar O, Ahsen A, Günary S, Koyuncu T, et al Neutrophil-to-lymphocyte ratio in chronic obstructive pulmonary disease: a retrospective study. Inflammation. 2014; 37:374-380.

[5] Balta S, Celik T, Mikhailidis DP, Oturk C, Demirkol S, Aparci M, et al, The relation Between Atherosclerosis and the Neutrophil-to-lymphocyte ratio. Clin Appl Thromb Hemost. 2016; 22: 405-411.

[6] Paliogiannis P, Fois AG, Sotgia S, Mangoni AA, Zinnellu E, Pirina P, et al, Neutrophil-to-lymphocyte ratio and Clinical outcomes COPD: recent evidence and future perspective. Eur Respir Rev. 2018; 27: 170113.

[7] Gasparyan AY, Ayvazyan L, Mukanova U, Yessirkepov M, Kitas GD. The Platelet-to-Lymphocyte Ratio as an Inflammatory Marker in Rheumatic Diseases. Ann Lab Med. 2019; 39:345-357.

[8] Vogelmeier CF, Criner GJ, Martine FJ, Anzueto A, Barnes PJ, Bourbeau J, 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 1;195: 557-582.

[9] Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates, et al., SERIES "ATA/ERS TASK FORCE: STANDARDISATION OF LUNG FUNCTION TESTING" Number 2 in this Series Standardisation of spirometry. Eur Respir J 2005; 26: 319–338.

[10] Yousef AA, Alkhiary W, Role of Neutrophil-to-lymphocyte ratio in prediction of acute exacerbation of chronic Obstructive Lung Disease. Egyptian Journal of Chest Diseases and Tuberculosis.2017; 66, 43-48.

[11] Aksoy E, Karakurt , Gungor S, Ockli B, Omen I, Yildirim E, et al., Neutrophil to lymphocyte ratio is a better indicator of COPD exacerbation severity in neutrophilic endotypes than eosinophilic endotypes. Int J Chron Obstruct Dis. 2018;13:2721-2730

[12] Rahimirad S, Ghaffary MR, Rahimirad MH, Rashidi F. Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute exacerbation of chronic obstructive pulmonary disease. Tuberk Toraks. 2017;65:25-31

[13] Furnutate R, Ishii T, Motegi T, Hattori K, Kusunoki Y, Gemma A, et al., The Neutrophil to Lymphocyte Ratio Is Related to Disease Severity and Exacerbation of Patients with chronic obstructive pulmonary disease. Intern Med. 2016;55: 223-229.

[14] Kalemci S, Akin F, Sarihan A, Sahin C, Zeybek A, Yilmaz N. The relationship between hematological parameters and the severity level of chronic obstructive lung disease. Pol Arch Intern Med. 2018;128:171-177.

[15] Teng F, Ye H, Xue T. Predictive value of neutrophil to lymphocyte ratio in patients with acute exacerbation of chronic obstructive pulmonary disease. PLoS One. 2018; 13:e02 04377.

[16] Li W, Ai X, Ni Y, Ye Z, Liang Z. The Association Between the Neutrophil-to-Lymphocyte Ratio and Mortality in Patients With Acute Respiratory Distress Syndrome. A Retrospective Cohort Study. Shock. 2019; 51: 161–167.

[17] Lee H, Um SJ, Kim YS, Kim DK, Jang AS, Choi HS, et al., Association of the Neutrophil-to-Lymphocyte Ratio with Function and Exacerbation in Patients with Chronic Obstructive Pulmonary Disease. PLoS ONE. 2016; 11: e0156511.

[18] Lee SJ, Lee HR, Lee TW, Ju S, Lim S, Go Sl 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: 891–898.

[19] Tanriverdi H, Örnek T, Erboy F, Altinsoy B, Uygur F, Atalay F, et al., Comparison of diagnostic values of procalcitonin, C-reactive protein and blood neutrophil/ lymphocyte ratio level in predicting bacterial infection in hospitalized patients with acute exacerbation of COPD. Wien Klin Wochenschr. 2015; 127: 756-763.

[20] de Jager CP, Waver PC, Gemenn EF, Kusters R, van Gageldonk-Lafeber AB, van der Poll T, et al., The neutrophil-lymphocyte count ratio in patients with community-acquired pneumonia. PLoS One. 2012; 7: e46561.

[21] de Jager CP, van Wijil PT, Mathoera RB, de Jongh-Leuvenink J, van der Poll T, Waver PC. Lymphocytopenia and neutrophil-lymphocyte count ratio predict bacteremia better than conventional infection markers in an emergency care unit. Crit Care. 2010; 14: R192.

[22] van de Geijn GM, van Denker S, Meuliman-van Waning V, Koeleman HG, Birnie E, Braunstahl GJ, et al., Evaluation of new laboratory tests to discriminate bacterial from nonbacterial chronic obstructive pulmonary disease exacerbations. Int J Lab Hematol. 2016; 38: 616–628

[23] Fün Sahin, Ayse Filiz Kosar, Aslan Buru Aslan, Burcu Yiğitbas Uslu. Serum biomarkers in patients with stable and acute exacerbation of chronic obstructive pulmonary disease: a comparative study. J Med Biochem. 2019; 38: 1–9.

[24] Karatas M, Gündüzöz M, Özis TN, Özakinci OG, Ergün D. Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio as hematological indices of the inflammatory response in ceramic workers' silicosis. Clin Respir J. 2019;13: 159-165.

[25] Barnes PJ, Celli BR. Systemic manifestation and comorbidities of COPD. European Respiratory Journal. 2009; 33: 1165-1185

[26] Rhee H, Love T, Harrington D. Blood Neutrophil Count is Associated with Mass Index in Adolescents with Asthma. JSM Allergy Asthma. 2018; 3: 1019