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Novel markers for chronic obstructive pulmonary disease monitoring: Glasgow Prognostic Score and neutrophil to lymphocyte ratio

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ABSTRACT

Aims: Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease characterized by persistent airflow limitation, frequent exacerbations, and respiratory symptoms. In this study, the usability of neutrophil to lymphocyte ratio (NLR) and Glasgow Prognostic Score (GPS) as markers to determine exacerbation patients, exacerbation severity and length of hospital stay in COPD patients was investigated.

Methods: 56 patients hospitalized for COPD exacerbation and 17 stable COPD patients evaluated in the outpatient clinic were included in the study. NLR and GPS were calculated for all patients. The relationship between NLR and GPS with the duration of hospitalization due to COPD exacerbation and the severity of exacerbation and the relationship between NLR with stable COPD patients and exacerbation patients were examined.

Results: The mean age of the patients was 64.9 years, and the mean cigarette consumption was 40.8 packs/year. The patients' mean FEV1, FVC, and FEV1 / FVC values were 46.2±21.6%, 67.6±26.4%, and 53.7±14.1%, respectively. NLR and GPS were determined to be statistically different between exacerbation patients and stable patients, and as the severity of exacerbation increased, the average NLR level increased significantly. When the relationship between NLR and GPS levels with the length of hospitalization was examined, a statistically significant relationship was found between both parameters with the length of stay.

Conclusion: It is thought that NLR and GPS levels can be used as an essential parameter in differentiating stable and exacerbation patients in COPD, determining the severity of exacerbation, and predicting hospitalization durations due to exacerbation.

Keywords: Chronic obstructive pulmonary disease, exacerbation, Glasgow Prognostic Score, neutrophil to lymphocyte ratio

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung condition characterized by chronic respiratory symptoms due to abnormalities of the airways and/or alveoli that cause persistent, often progressive, airflow obstruction.[1] Definitive diagnosis of COPD is made by determining postbronchodilator FEV_1/FVC (forced expiratory volume in one second/forced vital capacity) <70% by spirometry.[2] Since 2011, the Global Initiative For Chronic Obstructive Lung Disease (GOLD) guidelines have recommended the use of the ABCD classification for disease staging, which evaluates not only pulmonary function tests but also symptom levels and exacerbation risk together. As of 2023, these guidelines have updated treatment algorithms by merging groups C and D into a new group E, categorizing cases with a high risk of exacerbation as a single group, regardless of symptom severity.[2]

Exacerbations of COPD (E-COPD) are episodes of acute respiratory symptoms worsening often associated with increased local and systemic inflammation. E-COPD are key events in the natural history of the disease because they impact significantly on the health status of the patient, enhance the rate of lung function decline, worsen the prognosis of the patient and are associated with most of the healthcare costs of COPD.[2] Determining the severity of E-COPD with Anthonisen criteria play an important role in the course of COPD. Based on these criteria, exacerbations can be classified as type I, type II, and type III according to the presence of three basic criteria such as dyspnea, sputum purulence, and increase in sputum amount.[3] But these criteria are not an objective tool for determining the severity of exacerbation and management of treatment plans. As a subclinical inflammatory marker, neutrophil to lymphocyte

ratio (NLR) has become widespread use in recent years, especially in the evaluation of prognosis and progression of several chronic inflammatory diseases and malignancies.[4,5]

Glasgow Prognostic Score (GPS), a new inflammation-based indicator, derived from the calculation by serum albumin level and C- reactive protein (CRP)[6] and has been simply and inexpensively used as a scoring system to determine survival in several malignancies such as colorectal[7,8], gastro-esophageal[9,10], pancreatic[11] cancers, non-small cell lung cancer[12] and COPD.[13]

This study aimed to investigate the role of inflammatory markers such as NLR and GPS to predict COPD exacerbation, exacerbation severity, as well as the length of hospital stay in E-COPD patients.

METHODS

Ethics

The study was carried out with the permission of the Süleyman Demirel University Hospital Scientific Researches Evaluation and Ethics Committee (Date: 22.01.2019, Decision No: 12743). We obtained an informed consent form from all patients for procedure. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients and Patient Recruitment

Retrospective analysis was conducted on E-COPD patients hospitalized and S-COPD patients admitted to the outpatient clinic in the Chest Diseases Department of Süleyman Demirel University Hospital between January 2017 and October 2018. Patients with acute and/or chronic pulmonary thromboembolism, obstructive sleep apnea, connective tissue and inflammatory bowel diseases, patients with any history of lung cancer, and active pulmonary tuberculosis were not included in the study. Demographic characteristics of all patients, history for smoking habits, presence of comorbidities, pulmonary function tests, arterial blood gas analyses, calculated NLR, and GPS from routine laboratory tests were recorded.

Definition of Exacerbation or Stable Phases of COPD

COPD was defined according to the GOLD guidelines.[2] Exacerbation of COPD was defined as continuously (48 hours or more) worsening of symptoms such as dyspnea, cough, or sputum production that require increased treatment.[2,14] Exacerbation severity was defined according to the Anthonisen criteria.[3] Stable phase of COPD (S-COPD) was defined as a lack of evidence of exacerbation for four weeks before admission.[15]

Assessment COPD Symptoms

COPD symptoms were assessed by using the Turkish version mMRC dyspnea scale and COPD assessment test (CAT). COPD patients were classified using both post-bronchodilator FEV_1% predicted spirometry results and using exacerbation history and COPD symptoms to COPD A, B, C, and D groups according to the GOLD 2018 multidimensional approach.[16]

Length of Hospital Stay

Length of hospital stay was calculated as the difference between the calendar date of admission and discharge. The time of discharge from the hospital was made according to predefined criteria by Turkish thoracic society COPD working group.[17]

Pulmonary Function Testing

To detect the presence of persistent airflow limitation which was accepted as post-bronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio of <0.7, a spirometry and bronchodilator reversibility testing was performed according to the American thoracic society/European respiratory society (ATS/ERS) guideline.[18] Pulmonary function tests were performed at the admission of the outpatient clinic for S-COPD patients and the end of exacerbation therapy for E-COPD patients just before the discharge from the pulmonary clinic.

Laboratory Studies, and Preparation of Serum Samples

Venous blood samples of patients were drawn for routine biochemical tests and complete blood count (CBC). CBC was measured by an automatic blood counter (The Backman Coulter Unical DxH800, Backman Coulter, Miami, FL, USA). C-reactive protein (CRP) levels were determined by nephelometric method (BNTM II, Hamburg, Germany). NLR and GPS were calculated using serum albumin and CRP levels in COPD patients. The GPS calculation was done as previously defined, and was shown below: Score 0: Normal CRP (≤10.0 mg/L) and normal albumin level (≥3.5mg/dl). Score 1: One of these parameters is abnormal [elevated CRP (>10.0 mg/L) or hypoalbuminemia (<3.5mg/dl)]. Score 2: Elevated CRP (>10.0 mg/L) and hypoalbuminemia (<3.5mg/dl).[7]

For arterial blood gases analyses blood samples of the patients with E-COPD was drawn while the patient was under rest and sitting position, and breathing room air. A blood gas analyzer was used for measurement of blood samples (Roche OMNI C; Roche Diagnostics, Mannheim, Germany).

Statistical Analysis

The data analysis of the study was carried out by using the statistical package for the social sciences (SPSS) 20.0 program for Windows (IBM Inc, Chicago, Il, USA). For continuous numerical variables, the Kolmogorov-Smirnov test revealed that most of the variables were not distributed normally. For this reason, the Mann-Whitney U method and the Kruskal-Wallis method were used for the comparisons of two independent groups and multiple groups, respectively. Monte Carlo corrected chi-square analysis was used to determine the relationships between categorical variables. ROC curves were calculated to determine the factors on the duration of hospitalization, and the differential diagnosis rates were determined. Kaplan-Meier survival analysis was performed; survival curves were created for NLR. In the whole study, the type-I error rate was accepted as 5% and a value of $p<0.05$ was considered as statistically significant.

RESULTS

A total of 73 COPD patients were included in the study; 56 (76.7%) patients were hospitalized due to acute exacerbation, and 17 (23.3%) were admitted to the outpatient clinic in a stable period. Sixty-nine (94.5%) of the patients were male, 4 (5.5%) were female, mean age was 64.9±9.1 years

and average cigarette consumption was 40.8±28 packed/year. Comorbidities were determined in 27 (48.2%) of the patients. The most prevalent comorbidities were hypertension (n=11; 19.6%), congestive heart failure (n=8; 14.3%), diabetes mellitus (n=7; 12.5%), and coronary artery disease (n=6; 10.7%), respectively. Demographic characteristics, symptom scores, spirometric values and some laboratory parameters of E-COPD and S-COPD patients are given in **Table 1**.

As expected, the mean CAT symptom score and mean mMRC score were found to be high in E-COPD patients compared to S-COPD patients (p=0.001 and p=0.001) (**Table 1**). COPD stages of the patients according to airflow limitation on PFT were as follows; 6 (8.2%) stage I, 23 (31.5%) stage II, 22 (30.1%) stage III, and 20 (27.4%) stage IV. It was observed that there was a statistically significant difference between the stage of S-COPD patients and E-COPD patients, and that airflow limitation was more severe in E-COPD patients (p=0.006). According to the GOLD multidimensional approach, 50 (68.5%) of the patients were D group, 4 (5.5%) group C, 6 (8.2%) group B, and 13 (17.8%) group A. A statistically significant difference was observed between the stages of S-COPD patients and E-COPD patients (p<0.001).

A statistically significant difference was observed in NLR levels between S-COPD patients (2.99±1.73) and E-COPD patients (8.89±9.85) (p < 0.001) (**Table 1**). Also, it was observed that the cut-off NLR level determined as 5.45 had 57.14% sensitivity and 94.12% specificity in distinguishing stable and exacerbation patients (**Figure 1**).

The mean GPS value of all patients was 0.90±0.78, and the mean GPS value of E-COPD patients was statistically higher than S-COPD patients (p=0.001) We found that most of the S-COPD patients (76.5%) had GPS 0, but most of the E-COPD patients (76.8%) had GPS 1 or GPS 2 (p<0.001) (**Table 1**).

When we evaluated the exacerbation severity according to the Anthonisen criteria type I, type II, and type III exacerbations were detected in 19 (33.9%), 16 (28.9%), and 21

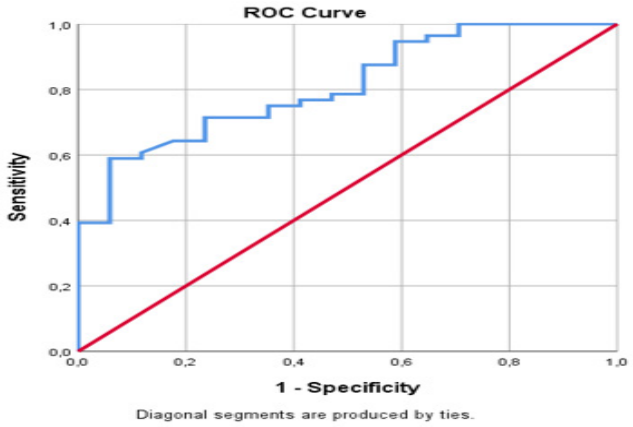

Figure 1. Sensitivity and specificity of NLR 5.45 in separating exacerbation and stable patients
NLR: Neutrophil to lymphocyte ratio

(37.5%) patients with hospitalized E-COPD, respectively. We found a statistically significant difference at the mean NLR levels among the exacerbation groups in which the mean NLR levels were 12.1±8.6, 7.6±8.4, and 6.2±3.9 in patients with type I, type II, and type III exacerbations, respectively (p=0.013) (**Table 2**). We found that the cut-off value of NLR level, which was determined as 7.65, was able to distinguish between severe and moderate/mild exacerbations in E-COPD patients with 65% sensitivity and 19% specificity. There was statistically significant relationship between exacerbation severity and GPS (p=0.011). Exacerbation severity and associated parameters are shown in **Table 2**.

When the relationship between NLR level and GPS was examined, it was found that most of the cases with NLR <7.65 were in the GPS 1 and 0 group, and those with NLR ≥7.65 were in the GPS 2 group (p=0.002) (**Table 3**).

We found no statistical significant relationships between $PaCO_2$ and PaO_2 levels in arterial blood gas analysis either with NLR or GPS values in patients with E-COPD. Among the hospitalized E-COPD patients, the mean length of stay was 10.2±3.4 days and was correlated with the exacerbation severity (r=0.332, p=0.012), and GPS (r=0.266, p=0.047),

Table 1. Demographic characteristics and laboratory parameters of E-COPD and S-COPD patients

		All patients (n=73) Mean±SD	E-COPD patients n=56 Mean±SD	S-COPD patients n=17 Mean±SD	p#
Age (years)		64.9±9.1	65.9±8.3	60.2±10.5	0.044
Gender (male/female)		69/4	53/3	16/1	0.399
Smoking history (packed/year)		40.8±28	38.4±28.1	48.5±27	0.934
CAT score		20±9.6	22.8±8.5	10.8±6.8	0.001
mMRC scale		2.35±1.21	2.60±1.18	1.52±0.94	0.001
FEV_1 (%)		46.2±21.6	42.3±20.6	58.1±20.8	0.009
FVC (%)		67.6±26.4	61.7±22.4	85.9±30.2	0.003
FEV_1/FVC		53.7±14.1	53.5±15	54.3±10.8	0.722
WBC (10^3/mm^3)		10.43±4.2	11.02±4.5	8.45±1.9	0.027
CRP (mg/L)		50.1±66.2	57.0±67.4	22.3±54.9	0.001
NLR		7.5±9.0	8. 9±9.8	2.99±1.7	<0.001
GPS		0.90±0.78	1.07±0.73	0.35±0.70	0.001
GPS groups*	GPS 0	26 (35.6%)	13 (23.2%)	13 (76.5%)	<0.001§
	GPS 1	28 (38.4%)	26 (46.4%)	2 (11.8%)	
	GPS 2	19 (26%)	17 (30.4%)	2 (11.8%)	

* Values are represented as count and percentages. E-COPD: Exacerbations of chronic obstructive pulmonary disease, S-COPD: Stable phase of chronic obstructive pulmonary disease, CAT: COPD assessment test, CRP: C-reactive protein, FEV1: Forced expiratory volume in 1 second, FVC: Forced expiratory capacity, FEV_1/ FVC: Forced expiratory volume in 1 second, forced expiratory capacity ratio, GPS: Glasgow Prognostic Score, mMRC: Modified medical research council, NLR: Neutrophil to lymphocyte ratio, WBC: White blood cell count, # Mann-Whitney U test, p<0.05, § Chi-square test

Table 2. Evaluation of exacerbation severity and associated parameters

		Type I mean±SD	Type II mean±SD	Type III mean±SD	p
Number of patients**		21 (37.5%)	19 (33.9%)	16 (28.9%)	-
Age (years)		69.5±7.9	63±8.4	64.7±7.2	**0.025***
FEV_1 (% predicted)		41.8±18.5	47.5±21.2	37.2±27.2	0.193
FVC (% predicted)		61.9±23.6	68.7±18.5	53.6±23.5	0.222
FEV_1/FVC		52.4±14.0	53.5±14.8	54.6±17.2	0.703
WBC (10^3/mm^3)		12.09±5.6	10.90±3.8	9.77±3.5	0.461
CRP (mg/L)		84±77.8	42.1±46.2	39.2±66.1	**0.027***
NLR		12.1±8.6	7.6±8.4	6.2±3.9	**0.013***
GPS		1.33±0.6	1.05±0.62	0.75±0.85	**0.011***
GPS groups**	GPS 0	2 (9.5%)	3 (15.8%)	8 (50.0%)	**0.021§**
	GPS 1	10 (47.6%)	12 (63.2%)	4 (25.0%)	
	GPS 2	9 (42.9%)	4 (21.1%)	4 (25.0%)	
PaO_2 (mmHg)		59.2±16.6	64.6±16.8	59.3±12.1	0.434
$PaCO_2$ (mmHg)		37.2±8.6	38.6±6.9	36.7±7.4	0.652
Length of stay (days)		12.1 ±3.3	9.1±2.8	9.0±3.2	**0.008***

CRP: C-reactive protein, FEV1: Forced expiratory volume in 1 second, FVC: Forced expiratory capacity, FEV1/FVC: Forced expiratory volume in 1 second, forced expiratory capacity ratio, GPS: Glasgow Prognostic Score, NLR: Neutrophil to lymphocyte ratio, PaO2: Partial pressure of oxygen in arterial blood, PaCO2: Partial pressure of carbon dioxide in arterial blood, WBC: White blood cell count,* Kruskal-Wallis test, p<0.05, § Chi-square test, ** Values are represented as count and percentages

Table 3. Relationship between NLR and GPS

	GPS			p
	0	1	2	
NLR (mean±SD)	4.71±3.99	5.84±4.75	13.82±14.53	**0.001***
NLR <7.65 (n, %)	23 (41.1%)	24 (42.8%)	9 (16.1%)	**0.002#**
NLR ≥7.65 (n, %)	3 (17.7%)	4 (23.5%)	10 (58.8%)	

NLR: Neutrophil to lymphocyte ratio, GPS: Glasgow Prognostic Score, SD: Standard deviation, * Kruskal-Wallis test, p<0.05, # Chi-Square p<0.05

but not with NLR (r=0.217, p=0.107). In patients with type I exacerbation length of hospital stay was more prolonged compared to other exacerbation groups (12.1± 3.3 days, 9.1±2.8 days, and 9.0±3.2 days for type I, type II, and type III exacerbation groups, respectively) (p=0.008). We found that length of hospital stay was more prolonged in patients with NLR≥7.65 compare to those with NLR <7.65 (9.3±3.1 days and 12.3±3.2 days, respectively) (p = 0.003) (**Figure 2**). Length of hospital stay was also longer in patients with GPS ≥ 1 compare to those with GPS=0 (10.8±3.2 days and 8.1±3.3 days, respectively) (p=0.045).

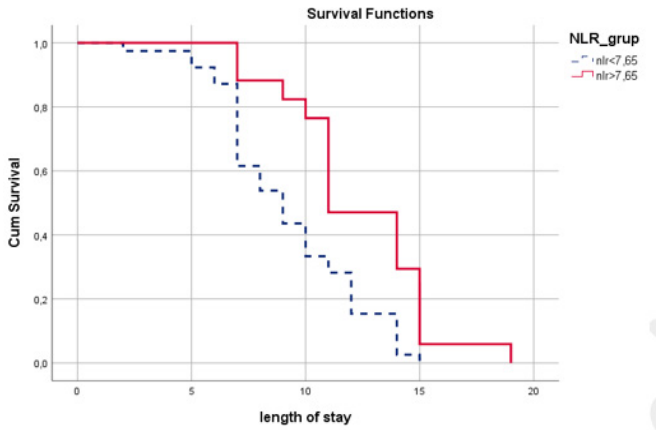

Figure 2. The duration of hospitalization of patients with NLR ≥7.65 and NLR <7.65
NLR: Neutrophil to lymphocyte ratio

In univariate analysis, age, the presence of comorbidities, $PaCO_2$, PaO_2, Leukocyte, neutrophil, and eosinophil counts, FEV_1, FVC, FEV_1/FVC, NLR, and GPS were predictors with prolonged length of hospitalization. In multiple logistic regression analysis, only NLR was identified as independent predictor (R^2=0.096, p=0.032).

DISCUSSION

In this study, the effects of NLR and GPS in distinguishing patients with exacerbations from stable patients in COPD, determining the severity of exacerbations and on the duration of hospitalization in patients with exacerbations were investigated. It was determined that NLR and GPS showed statistical differences between E-COPD and S-COPD patients and that the NLR value determined as 5.45 could be used as a cut-off to distinguish these patients. A significant difference was observed between the exacerbation severity groups and the GPS and NLR levels. In multivariate analyses, it was determined that the NLR level was associated with the duration of hospitalization and that there was a statistically significant difference between the cases below the NLR level determined as 7.65 and those above it.

COPD exacerbations are clinical conditions that progress in the form of clinical and functional deterioration in the course of the disease and negatively affect the course of the disease. During exacerbation periods, COPD patients may need additional treatment and hospitalization.[17] Therefore, the detection and management of exacerbations is an important issue in the field of chest diseases. In this study, two new parameters that can distinguish E-COPD patients from S-COPD patients were studied. It has been determined that both NLR and GPS levels show significant differences in exacerbation and stable patients and that these two patient groups can be separated with 57.14% sensitivity and 94.12% specificity with the NLR level determined as 5.45. There are many different studies conducted on NLR level, which is an inflammatory indicator, both in COPD and other inflammatory diseases. Hematological parameters are widely used cheap and easily accessible diagnostic tools. The NLR started to be used frequently as one of the indicators of systemic inflammation along with other inflammatory markers, and stated that NLR could be a good indicator in showing the presence of systemic inflammation in patients with COPD.[19] In the ECLIPSE study, (n=1755), 16 % of patients with COPD had the evidence of systemic inflammation based on leukocyte count, CRP, IL-6, IL-8, fibrinogen, and TNF-α levels.[20] It was shown that mortality rates and exacerbation frequency were higher in patients with systemic inflammation, despite similar lung functions.[21] Studies

were shown that NLR levels were higher in COPD patients compared to healthy individuals and can distinguish COPD patients in stable and exacerbated periods.[22,23] In a meta-analysis study the mean NLR level was found to be 2.62±2.26 in stable patients and 6.38±5.80 in exacerbation patients.[24] Compatible with the literature, we showed a significant difference in mean NLR levels between the patients with E-COPD (8.89±9.85) and S-COPD (2.99±1.73). In this study, the cut-off NLR level, which was determined as 5.45 by ROC analysis, was found to have 57.14% sensitivity and 94.12% specificity in differentiating the patients with E-COPD and S-COPD. In this study, as expected, the majority of hospitalized E-COPD patients (89.3%) were patients at high risk of exacerbation, classified as groups C and D according to the pre-GOLD 2023 reports and group E according to the post-2023 reports.[2,16] It is a well-known phenomenon that, patients who had more than two exacerbations in the last year had a higher rate of hospitalization due to exacerbation, and previous exacerbations are the strongest predictor of a patient's future exacerbations.[25]

Determining the severity of exacerbation is important in detecting the severity of the disease and planning appropriate treatment options. We used the Anthonisen criteria in our study to determine the severity of exacerbation.[3] 37.5% of the patients who received exacerbation treatment were classified as group I, 33.9% as group II, and 28.9% as group III. The relationship between exacerbation severity and NLR level was examined, it was observed that NLR levels were higher in patients with more severe exacerbations. Besides, it was found that there was a statistically significant relationship between the severity of exacerbation and the duration of hospitalization, and the longer the duration of the exacerbation, the longer the duration of hospitalization. In the study conducted by Akın et al.[26] 69.4% of exacerbation patients were group I, 22.6% were group II and 8.1% were group III It was observed that he/she was admitted to the hospital with exacerbation. In another study, it was shown that there was a statistically significant relationship between the NLR level and the severity of COPD, similar to our study.[22] In the study of Kalemci and his friends[27]; It was shown that there was a relationship between NLR level and lymphocyte number and COPD severity. In a systematic review examining the poor clinical outcomes of NLR in E-COPD patients (mortality, intensive care follow-up, need for mechanical ventilation, development of pulmonary hypertension, etc.), it was determined that high NLR values were an independent risk factor for poor clinical outcomes in logistic regression analyses in 10 out of 18 studies.[28] In a study examining GPS levels in patients with exacerbations, it was determined that high GPS was associated with poor clinical outcomes.[13] In this retrospective study, poor clinical outcomes of the patients were not evaluated, but the statistical significance of high NLR and GPS in those with high exacerbation severity also supports these findings.

In studies conducted, the length of hospital stay in COPD exacerbations (E-COPD) has been identified as an independent risk factor for the severity of the disease.[29-32] Therefore, assessing the duration of hospitalization is crucial. In this study, the average length of hospital stay for E-COPD patients was found to be 10.2±3.4 days. A correlation was observed between the length of stay and exacerbation severity as well as GPS levels. It was found that those with NLR levels above the cut-off value of 7.65 (as determined by ROC curve analysis) had significantly higher lengths of stay. Regression analysis revealed that NLR levels are an independent risk factor for prolonged hospital stay. Most studies on hospital stay in E-COPD patients have focused on demographic characteristics such as age and gender, as well as disease severity and stage, with relatively few studies examining laboratory markers. In a study by Liao et al.[33] a correlation between NLR levels and hospital stay duration was observed in E-COPD patients. Additionally, studies have shown a correlation between hospital stay duration and GPS levels in various diseases, especially hematological cancers.[34,35] NLR and GPS levels are believed to be two new parameters that could be used to predict the length of hospitalization and reflect the severity of the disease in COPD exacerbations.

Limitations

There are some limitations to our study. First, since the study was designed retrospectively, data were obtained from the patients' clinical records and patient files. Second, the small number of patients, especially S-COPD patients, can be considered. In addition, poor clinical outcomes (such as the need for intensive care or mechanical ventilation, pulmonary hypertension and mortality) for E-COPD patients were not evaluated.

CONCLUSION

In conclusion, it has been shown that NLR and GPS can be used as important parameters in distinguishing stable patients from patients with exacerbations in the course of COPD, determining the severity of exacerbations, and predicting the duration of hospitalization due to exacerbations. We believe that the easy use of GPS and NLR should make the use of these two parameters widespread in the course of COPD and support them with larger scale prospective studies.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Süleyman Demirel University Hospital Scientific Researches Evaluation and Ethics Committee (Date: 22.01.2019, Decision No: 12743).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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