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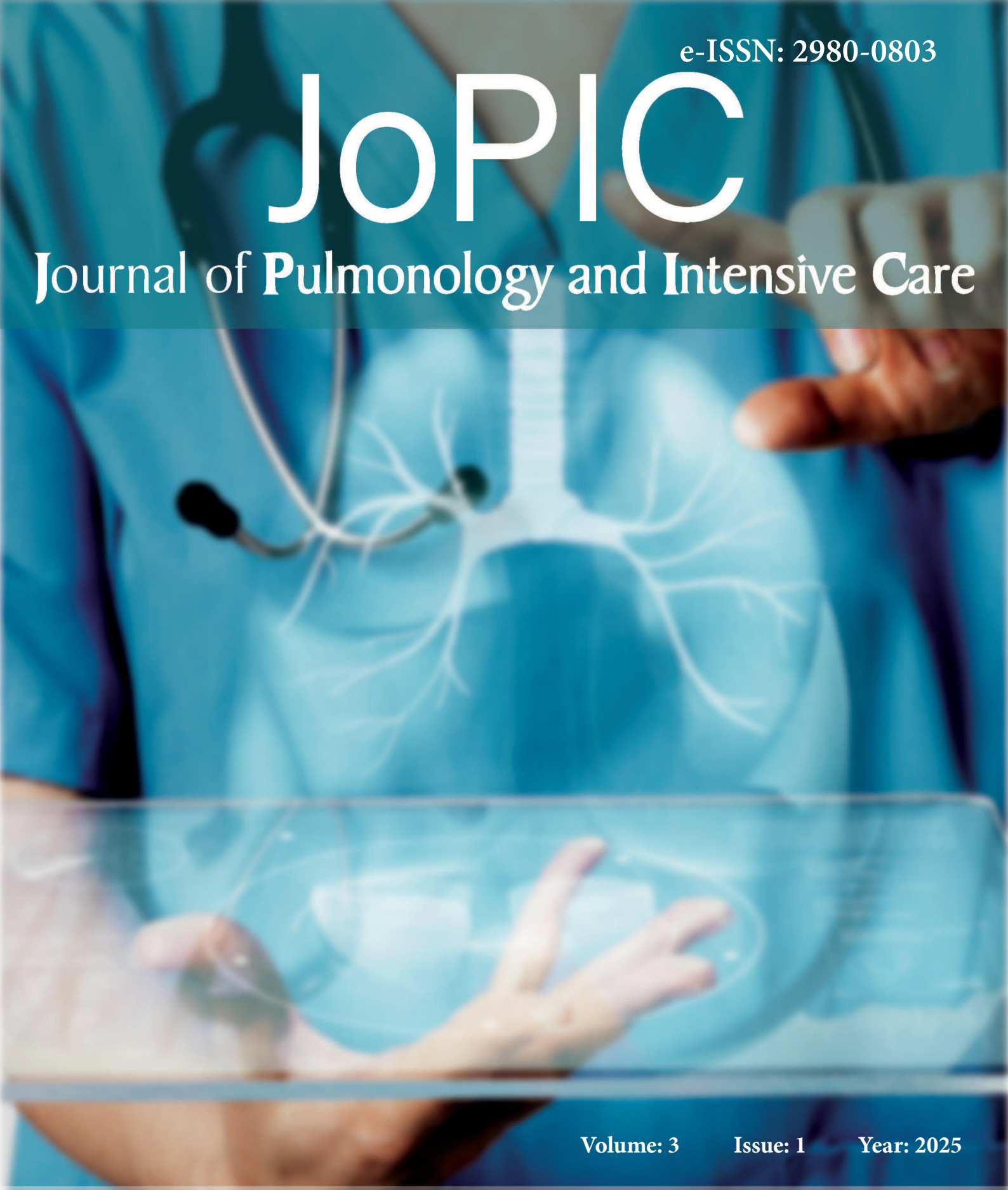

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EDITORIAL

Dear Colleagues,

As of February 2025, we have completed the second year of our journal's publication life. We have published the ninth issue of Journal of Pulmonology and Intensive Care (JoPIC) under the shield of MediHealth Academy. In addition to all researchers, referees and editorial board who contributed to the preparation of the journal; we would like to thank the printing team for their effort in preparing it for publication. This ninth issue includes two original research, two case reports and a review. Periodicals are popular with their readers and researchers. In the upcoming period, with your support, our goal is for JoPIC to be indexed in nationally and internationally accepted scientific indexes. I would like to thank you in advance for your contribution.

Assoc. Prof. Berna Akıncı ÖZYÜREK
Editor in Chief

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Original Article

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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

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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

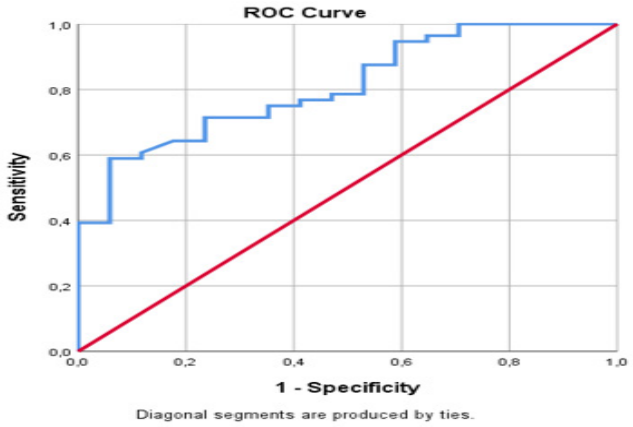

Figure 1. Sensitivity and specificity of NLR 5.45 in separating exacerbation and stable patients
NLR: Neutrophil to lymphocyte ratio

(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).

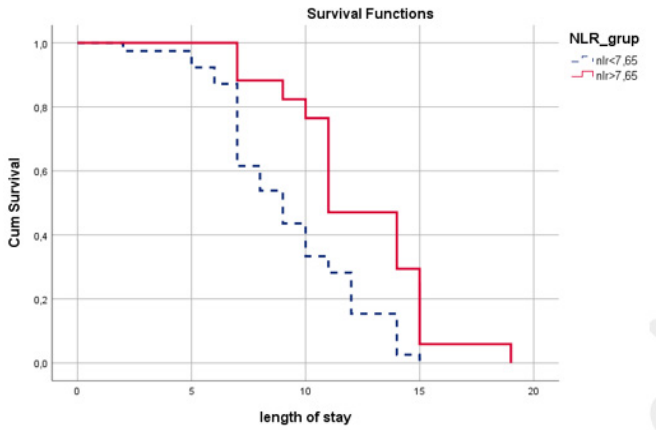

Figure 2. The duration of hospitalization of patients with NLR ≥7.65 and NLR <7.65
NLR: Neutrophil to lymphocyte ratio

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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Pre-pandemic early viral pneumonias; could we have encountered COVID-19 before? Accompanying a diagnostic model

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ABSTRACT

Aims: COVID-19 shows overlapping clinical and radiological findings with other viral pneumonias. This study designed to explore the likelihood of the existence of COVID-19 pneumonia in our country before March 11th, date of first official COVID-19 case detected in Turkey, by using a diagnostic model designed with radiologic and laboratory findings.

Methods: 273 patients with pre-diagnosis of viral pneumonia were aggrouped according to hospitalization date (before and after 11 March), naso-oropharyngeal swab PCR results. Thoracic tomographies, C-reactive protein (CRP), leukocyte, lymphocyte, monocyte, eosinophil, platelet values of all patients were evaluated.

Results: Laboratory findings of lymphocyte, eosinophil counts ($p<0.05$) were significantly low; radiologic findings of round opacity, cobblestone, nodüle, subpleural line were significant in COVID-19 group ($p<0.05$). 'Round opacity', 'subpleural line', 'nodule', 'lymphocyte' variables were found to be statistically significant for final model ($p<0.05$). COVID-19 diagnosis possibility; increases 302.9% by 'round opacity', 355.6% by 'subpleural lines'; and decreases 59.1% by 'nodule' presence, 31.7% by one unit increase in lymphocyte level. Based on final model; 49.3% of the participants before 11 March 2020 were predicted to be positive for COVID-19.

Conclusion: According to these findings, we can say that COVID-19 patients existed before March 11th, 2020 in Turkey, for the first time. Also based on same diagnostic model; subpleural lines, presence of cobblestone, round opacity appearances and absence of nodules on tomography, and the presence of lymphopenia and eosinopenia in the cell count can also be used to support the diagnosis of COVID pneumonia.

Keywords: COVID-19, pre-pandemic viral pneumonia, radiology findings, laboratory findings, diagnostic model

INTRODUCTION

Nowel coronavirus infection, which was introduced to the world on January 5th, 2020 by World Health Organization (WHO), became a global health problem towards the end of January and it was identified as coronavirus disease 19 (COVID-19) on the February 11th, 2020.[1] The first official COVID-19 case was detected on March 11th, 2020 in our country and this is the date which WHO announced the pandemic.[1,2] Since the first emergence of this pandemic; early diagnosis of the disease and quarantining the infected person have been accepted as the most important steps towards controlling the outbreak.[3,4] Although the definitive diagnosis is based on PCR positivity[5], due to the high false negativity and low sensitivity of this test, and the need for special laboratory conditions; some diagnostic models ranging from 'rule-based scoring systems' to 'advanced machine learning models' which evaluate clinical condition, comorbidities, symptoms, laboratory and radiological findings of the patient has been used to calculate the disease risk.[6,7]

Another reason for the difficulty in diagnosis is that COVID-19 shows similar clinical and radiological findings with other viral pneumonias, especially Influenza A (H1N1), occurring in the same periods as COVID every year.[8-12] Common symptoms related to COVID-19 infection like fever, cough, fatigue, dyspnea, myalgia and rarely sore throat, chest pain, runny nose, conjunctival congestion, nausea, vomiting, diarrhea can be seen.[13] In our clinical practice, since January 2020, we have noted that the number of cases with clinical and radiological findings of viral pneumonia, but pathological agents that could not be identified with PCR, has increased. Based on this prediction and as the first study on this subject; we aimed to explore the likelihood of

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the existence of COVID-19 pneumonia in our country before March 11th, 2020.

METHODS

The study was conducted with the permission of University of Health Sciences Samsun Training and Research Hospital Non-interventional Clinical Researches Ethics Committee (Date: 30.06.2020, Decision No: 2020/10/5). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was designed retrospectively. We have included 120 patients who were hospitalized with clinically and radiologically proven viral pneumonia diagnosis and whose naso-oropharyngeal swab samples were taken between January 1st, 2020 and March 10th, 2020 and 168 patients who were diagnosed as COVID-19 and whose naso-oropharyngeal swab samples were taken between March 11th, 2020 and August 30th, 2020. Fifteen participants were excluded from the study because we could not reach their computerized tomography or laboratory findings.

In total, 273 patients were divided into two groups according to the date of March 11th, when the first COVID case has introduced in Turkey. Then these groups were categorized according to the PCR results (**Table 1**). Accordingly, group 1 included patients whose pathological agent were isolated in PCR testing before March 11th (n=36), group 2 patients whose pathological agent could not be identified in PCR testing before March 11th (n=79), group 3 included patients whose PCR tests were positive for COVID-19 after March 11th (n=83) and group 4 included patients whose PCR tests were negative for COVID-19 after March 11th (n=85) (**Table 1**).

Table 1. Study groups

All patients who have been included in the study (n=273)
1.Group: Pathological agent isolated with PCR before March 11th (n=36)
2.Group: Pathological agent couldn't be isolated with PCR before March 11th (n=69)
3.Group: Positive PCR result for COVID-19 after March 11th (n=83)
4.Group: Negative PCR result for COVID-19 after March 11th (n=85)

All scans were obtained using a 16-row multidetector scanner (Siemens Sensation 16, Erlangen, Germany) with the following parameters: 120 kVp, 150 mA, 1.5 mm collimation, 1.35:1 pitch, sharp kernel (B80f), reconstruction matrix of 512×512, slice thickness of 1.0 mm, and high spatial resolution algorithm.

Thoracic tomographies of all patients were independently evaluated by two different, blinded, 10-12 years experienced radiologists. Later, a council was held for the final report of the patients if there was no consensus. Each tomography was evaluated according to Fleischner society nomenclature and similar study recommendations.[15-17]

Tomographies were examined whether they have ground glass consolidation, distribution (peripheral, central, mixed), linear opacity, round opacity, cobblestone appearance, halo sign, tree-in-bud, interlobular septal thickening, bronchiectasis, cavitation, air bronchogram, nodule, subpleural line, lymphadenopathy, pleural thickening, pleural effusion and which lobe(s) involved (upper/middle/lower right and upper/lower left) (**Table 2**).

Table 2. Findings evaluated in tomographic scans

- Ground glass
- Consolidation
- Distribution (peripheral, central, mixed)
- Linear opacity
- Round opacity
- Cobblestone appearance
- Halo sign
- Tree-in-bud
- Interlobular septal thickening
- Bronchiectasis
- Cavitation
- Air bronchogram
- Nodule
- Subpleural line
- Lymphadenopathy
- Pleural thickening
- Pleural effusion
- Affected lobes (upper/middle/lower right and upper/lower left)

In all patients' blood tests; C-reactive protein (CRP), leukocyte, lymphocyte, monocyte, eosinophil, platelet values were included in the evaluations. We have also included neutrophil/lymphocyte, monocyte/lymphocyte, neutrophil/CRP, lymphocyte/CRP, eosinophil/CRP ratio evaluations during statistical analysis.

In the first stage, factors that differed significantly between COVID-19 groups (groups 3 and 4) were identified and logistic regression models were created by selecting these as independent variables. Based on the obtained predictive logistic regression model, the probability of having COVID-19 in patients with negative swab status before March 2020, namely group 2, was calculated. According to this probability, the possibility of encountering COVID-19 before March 11 was examined.

Statistical Analysis

In this study, we used the Fisher test for relations between categorical data and diagnosis of COVID-19 and an independent sample t-test for numerical measurements. Since the number of observations from COVID-19 diagnostic groups was n>30, a parametric method, t-test, was performed. Based on the obtained predictive logistic regression model, the probability of COVID-19 in the participant with a negative swap before March 2020 was calculated. Statistical analysis was performed using R-Project software (14) and IBM SPSS 22 program. Statistical test results were evaluated at a 95% confidence interval.

RESULTS

The median age of group 1 and 2 was 64.2, and the median age of group 3 and 4 was 54.8. Pathological agents isolated in the first group were; H1N1 (n=22), influenza B (n=2), rhinovirus (n=4), RSV A/B (n=3), corona NL63/HLU1 (n=3/1).

Laboratory Findings

Table 3 summarizes the results of the test hypothesis showing relations between laboratory findings including numerical measurements and COVID-19 diagnosis groups. According to test results, we found a statistically significant relation between COVID-19 groups and lymphocyte and eosinophil counts ($p<0.05$). Given the medians, patients who had a positive COVID-19 diagnosis had significantly lower lymphocyte and eosinophil levels.

Table 3. Statistical hypothesis test results for laboratory findings

Laboratory findings	COVID		p
	Positive (n=83)	Negative (n=85)	
Platelet	185 (95.1)	187 (134)	0.917
Neutrophil	41.5 (110)	70.5 (108)	0.129
Lymphoccyte	1.84 (1.45)	3.26 (3.01)	**0.001**
Monocyte	0.83 (0.96)	1.09 (0.90)	0.117
Eosinophil	0.18 (0.31)	0.34 (0.41)	**0.011**
C-reactive protein (CRP)	22.7 (31.1)	27.8 (64.1)	0.561
Neutrophil/lymphocyte	11.9 (25.2)	15.5 (21.6)	0.374
Monocyte/lymphocyte	0.57 (0.64)	0.45 (0.42)	0.221
Neutrophil/CRP	306 (886)	422 (810)	0.437
Lymphosite/CRP	5.13 (14.8)	12.0 (26.3)	0.063
Eosinophil/CRP	0.89 (2.47)	1.46 (2.79)	0.216

Data are represented as mean (standart deviation)

Radiological Findings

Table 4 shows the test hypothesis results of the relationships between the radiology findings including categorical data and the COVID-19 diagnosis groups. According to test results, we found a statistically significant relation between COVID-19 groups and cases with round opacity, cobblestone, nodule and subpleural line ($p<0.05$). Considering the percentages, the probability of having 'round opacity' and 'subpleural line' is higher in group 3 than in group 4. But the probability of having 'cobblestone' and 'nodule' is lower in group 3 in comparison to group 4.

Modelling

In **Table 5**, using the COVID-19 diagnostic groups as dependent variables a logistic regression model (full model) is created for the factors that are significant in the test hypothesis findings. Because 'eosinophil' and 'cobblestone' variables were found to be statistically insignificant a new model was developed by removing them from the model (final model). 'Round opacity', 'subpleural line', 'nodule' and 'lymphocyte' variables were found to be statistically significant in this model ($p<0.05$). According to the odds ratio, patients who had round opacity are 302.9% more likely to have a positive COVID-19 diagnosis than those who did not have it. Furthermore, we found that patients who had subpleural lines are 355.6% more likely to have a positive COVID-19 diagnosis. The presence of a nodüle decreases the likelihood of COVID-19 positivity by 59.1 percent. One unit increase in lymphocyte level causes a 31.7% decrease in the probability of a positive COVID-19 diagnosis.

Table 6 shows the performance metric results for the final logistic regression model. Based on these results, the accurate classification rate of the model established to predict the diagnosis of COVID-19 is 70.4%, the sensitivity is 68.3%, and the specificity is 72.5%. The Nagelkerke-R^2 value of the model is at the level of 31% and is far from zero. According to the performance metrics, the prediction performance of the model was found to be sufficient and all the parameters included in the model are significant. The C index value of the logistic regression model is 0.778 and the model's power to differentiate COVID-19 patients from healthy individuals is quite sufficient.

In this logistic regression model, we used 'round opacity', 'subpleural line', 'nodule' and 'lymphocyte' values of the participants before March 11th, 2020 as independent variables

Table 4. Statistical hypothesis test results for tomographic findings

Tomographic findings	COVID		p
	Positive (n=83)	Negative (n=85)	
Ground glass			
No	20.5%	20.0%	1.000
Yes	79.5%	80.0%	
Consolidation			
No	86.7%	76.5%	0.129
Yes	13.3%	23.5%	
Distribution			
Absent	16.9%	22.4%	
Peripheral	37.3%	21.2%	0.132
Central	2.41%	2.35%	
Mixed	43.4%	54.1%	
Linear opacity			
No	68.7%	81.2%	0.090
Yes	31.3%	18.8%	
Round opacity			
No	44.6%	74.1%	**<0.001**
Yes	55.4%	25.9%	
Cobblestone			
No	83.1%	97.6%	**0.003**
Yes	16.9%	2.35%	
Halo sign			
No	94.0%	91.8%	0.797
Yes	6.02%	8.24%	
Tree-in-bud			
No	96.4%	87.1%	0.056
Yes	3.61%	12.9%	
Bronchiectasis			
No	96.4%	87.1%	0.056
Yes	3.61%	12.9%	
Interseptal thickening			
No	81.9%	80.0%	0.903
Yes	18.1%	20.0%	
Cavitation			
No	100%	98.8%	1.000
Yes	0.00%	1.18%	
Air bronchogram			
No	83.1%	82.4%	1.000
Yes	16.9%	17.6%	
Nodule			
No	77.1%	54.1%	**0.003**
Yes	22.9%	45.9%	
Subplevral line			
No	66.3%	82.4%	**0.027**
Yes	33.7%	17.6%	
LAP			
No	91.6%	81.2%	0.083
Yes	8.43%	18.8%	
Pleural thickening			
No	89.2%	80.0%	0.153
Yes	10.8%	20.0%	
Pleural effusion			
No	96.4%	90.6%	0.228
Yes	3.61%	9.41%	
Right middle			
No	42.2%	38.8%	0.776
Yes	57.8%	61.2%	
Right lower			
No	27.7%	38.8%	0.173
Yes	72.3%	61.2%	
Right upper			
No	41.0%	38.8%	0.900
Yes	59.0%	61.2%	
Left upper			
No	37.3%	49.4%	0.155
Yes	62.7%	50.6%	
Left lower			
No	31.3%	44.7%	0.104
Yes	68.7%	55.3%	

Table 5. Logistic regression analysis results for COVID-19 diagnosis

Variable	Full model			Final model		
	Exp (β)	Wald	p	Exp (β)	Wald	p
(Intercept)	0.813	-0.467	0.640	0.690	-0.879	0.380
Round opacity (yes)	0.334	-2.643	**0.008**	0.330	-2.725	**0.006**
Cobblestone (yes)	0.205	-1.901	0.057	-	-	-
Subpleural line (yes)	0.288	-2.624	**0.009**	0.281	-2.693	**0.007**
Nodule (yes)	2.404	2.054	**0.040**	2.447	2.139	**0.032**
Lymphocyte	1.475	2.195	**0.028**	1.464	2.992	**0.003**
Eosinphil	0.818	-0.254	0.799	-	-	-

Exp (β): Odds ratio

Table 6. Performance metric results for the final logistic regression model

Metric	p
Accuracy	0.704
Sensitivity	0.683
Specificity	0.725
C index	0.778
Nagelkerke-R^2	0.310

and estimated rate of COVID-19 diagnoses. Based on this logistic regression model, 49.3% of the participants before 11 March 2020 were predicted to be positive for COVID-19. According to these findings, we can say that COVID-19 patients existed before March 11th, 2020 in Turkey.

DISCUSSION

The goal of this study was to investigate the unproven existence of COVID in the patients who were diagnosed with radiologically or clinically proven viral pneumonia but the pathological agent could not be identified before the announcement of the first COVID case in Turkey on January 1th, 2020. For this purpose, we used a model based on the radiological and laboratory values of 168 patients who have positive or negative COVID-19 PCR results and found that before the 11th of March the probability of COVID in the viral pneumonia patients whose agent could not be isolated was 49.3%. This is the first known probability assessment study for our country.

Due to the low sensitivity and high false negativity of the PCR, the suspicion of COVID infection is frequently investigated with CT findings. Fang et al.[18] reported that the sensitivity of the first PCR was 71%. Some studies indicated >90%[19] and 97%[17] sensitivity of CT scans for the diagnosis of this disease. There have been many publications on radiological features thought to be specific for COVID pneumonia. Nevertheless, ground-glass opacity is the most striking feature for both COVID and other viral pneumonias. In a meta-analysis of 2738 patients in 13 studies[20]; ground-glass opacities, interlobular septal thickening, adjacent pleural thickening and air bronchogram and especially bilateral and lower lobe localized lesions were found to be significant for COVID.

In another meta-analysis comparing COVID-19 confirmed by PCR with other viral pneumonia[21]; the findings specific to COVID were stated as predominantly ground-glass opacity, secondly mixed pattern including consolidation, and thirdly bilateral and mostly lower lobe involvement. However, in non-COVID cases, mainly a mixed pattern consisting of ground glass and consolidation, ground glass in the second and bilateral and lower lobe involvement in the third was detected. In another study comparing CT findings of COVID-19 and H1N1 infections by Yin at al.[22]; peripheral or peribronchovascular distribution, ground-glass opacity, consolidation, subpleural line, air bronchogram appearances did not show a statistically significant difference between the groups. Since the patients included in our study were hospitalized with suspicion of viral pneumonia, especially with a ground-glass appearance in their clinics and tomographies, and PCR samples were taken after hospitalization; ground-glass opacities and predominant involvement of any lobe were statistically significant in our patient group.

Wu at al.[23] categorized 130 patients whose COVID infection was confirmed by an antibody test according to radiological findings, first CT was taken in 1-20 days after the onset of symptoms and control CT's were taken in 3-27 days. They mentioned three different distribution according to this categorization. Lobular distribution; is the most common form in which the virus settles in the center of the lobule and rapidly spreads to the environment creating a ground-glass pattern. Diffuse distribution; is the form in which both lobule and subpleural space are involved. Subpleural distribution; starts from blood vessel and lymphatics rich interstitium of the lobules located in subpleural areas and causes a more serious inflammatory response. If the virus spreads through the interlobular especially perialveolar interstitium, lymphatic drainage of this area is either towards the interseptal area or subpleural area. Since it cannot extend distally in the subpleural area, progression is observed parallel to the pleura, which causes subpleural lines. Wu at al.[23] mentioned that this appearance is characteristic for the novel coronavirus pneumonia but is not specific as it can also be seen in other viral pneumonias. In our study, however, subpleural streaking was detected as a specific finding for COVID-19 infection (p=0.007) and was used in the final model. In the same study again, as in severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS), it has been referred that 'cobblestone appearance' is an important marker of interlobular septum involvement, but it is nonspecific for other viral pneumonias. In our study, the incidence of 'cobblestone appearance' was lower in the COVID-19 positive group than in the negative group.

Wu et al.[23] examined the follow-up CT images of 35 patients; they interpreted regression of ground-glass opacity, consolidation, corner contraction and retractions, subpleural line or fiber strips and bronchiectasis as changes due to

organization. It has been stated that consolidation was more frequent in the late phases of COVID and the patient group above 50 years of age.[24] Interlobular septal thickening may indicate the presence of interstitial fluid, cell infiltration or fibrosis, as well as parainfluenza, hantavirus and SARS infections.[25] In our COVID-19 positive patient group, consolidation and interseptal thickening were not statistically significant.

While comparing CT findings of COVID-19 and *Influenza pneumonia*[26]; it has been mentioned that the presence of peripherally distributed round opacities and interlobular septal thickening and the absence of nodule and tree-in-bud appearance can be used to differentiate COVID-19 from influenza pneumonia. The size of the nodule can give an idea about the differential diagnosis of infectious causes and it has been previously reported that lesions below 1 cm may have a viral origin.[27] In the study of Pan et al.[24], while nodules were seen in 71% of the influenza infections, they were observed in only 28% of the COVID-19 infections. Also, Liu et al.[26] reported that a combination of some CT findings may be useful in differentiating COVID and influenza. These findings are listed as the presence of pure ground-glass/round opacity/interlobular septal thickening and absence of nodules; the presence of pure ground-glass and inter-lobular septal thickening; the presence of round opacity and interlobular septal thickening; and absence of pleural effusion. In our study, we have found that round opacity and subpleural line increased the possibility of having COVID by 302.9% and 355.6% respectively. Also, the presence of nodules decreased the possibility of having a positive diagnosis for COVID-19 by 59.1%. These three findings were used in modelling by providing sufficient reliability in logistic regression analysis (C index=0.078).

Studies have been conducted not only on radiologic findings but also on practical laboratory tests that can be used in the differential diagnosis when the patient presents with the first symptom. In a study designed fort his goal by Lia at al.[28], it has been reported that decreased leukocytes (<9.5 10^9/L), lymphopenia (<1.1 10^9/L), eosinopenia (<0.02 10^9/L), increased CRP (>4 mg/dl) were associated with COVID, particularly combination of eosinopenia and CRP elevation has 67.9% sensitivity and 78.2% specificity in terms of disease diagnosis.

Eosinopenia is seen in 50-70% of severe COVID patients. The underlying cause is uncertain, but there are some predictions. These are; decreased eosinophilopoiesis, defect in eosinophil release from bone marrow, increased eosinophil apoptosis due to IFN-1 released during acute infection.[29] The event of eosinophils binding to the virus and inactivating the virus[30], which has been shown in influenza A and respiratory syncytial virus (RSV) infections, may also be valid in COVID infections. Similar to eosinopenia, lymphopenia has also been found to be an independent risk factor for mortality in COVID.[31] Conditions causing lymphopenia can be listed as T-cell burnout, increase in lymphocyte proptosis and apoptosis, decrease in bone marrow suppression and release during cytokine storm.[32] In our study; eosinophils and lymphocytes were found to be significantly lower in COVID-19 patients, and they were found suitable for use only in the lymphopenia diagnosis model after logistic regression. In our study, eosinophils and lymphocytes were significantly lower in COVID-19 patients, and after logistic regression, they were only found suitable for use in the lymphopenia diagnosis model.

In the final model, we found that round opacity, subpleural line, nodule and lymphocyte were statistically significant. This model was used for the 2nd group (patients whose agent could not be isolated before March 11th) and the probability of COVID-19 was calculated as 49.3% (n=34). In a review examining models created for diagnosis, prognosis and mortality risk[6], such models were approached with bias and their routine use was not recommended because of not selecting control patients appropriately, exaggerated positive and sometimes suspicious results, and it was thought that they were entered the academic literature very quickly and there was an optimistic approach regarding their performance in cases where there was an urgent need for medical support. The goal of using a model in our study was to predict the probability in our previous patients and build this prediction on robust statistical data.

There are various publications that this novel type of coronavirus was found in nature before December 2019, and that causes disease. In their study, Forstera et al.[33] follow the phylogenetic network of the SARS-CoV-2 genome and after examining more than 10.000 phylogenetic studies of various organisms, they concluded that the final version of the virus that caused the infection emerged before December 24, 2019. Also, SARS-CoV-2 RNA was found in a water sample from November in Brazil.[34] Additionally, the COVID-19 antibody was detected in blood samples taken between December 2019 and January 2020 in the United States.[35]

Limitations

Our study has several limitations. First, only 273 patients were included. Larger studies might support these results. Second limitation was that samples from the pre-COVID period could not be serologically examined. However, with the high reliability of our statistical findings, our results support the possibility of this virus started to cause infection before the announced introduction date in our country.

CONCLUSION

Radiologic and laboratory findings can be useful in the early prediction and differentiation of COVID pneumonia and other viral pneumonias before the PCR results are obtained. Subpleural lines, presence of cobblestone, round opacity appearances and absence of nodules on tomography, and the presence of lymphopenia and eosinopenia in the cell count can also be used to support the diagnosis of COVID pneumonia.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of University of Health Sciences Samsun Training and Research Hospital Non-interventional Clinical Researches Ethics Committee (Date: 30.06.2020, Decision No: 2020/10/5).

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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Association between idiopathic pulmonary fibrosis and lung cancer

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ABSTRACT

The morbidity of lung cancer in patients with idiopathic pulmonary fibrosis (IPF) ranges from 3% to 22%, significantly shortening the lifespan. However, the mechanisms by which IPF increases morbidity and mortality in lung cancer are not well understood. Lung cancer with IPF is more frequently observed in the peripheral regions of the lungs and in honeycomb areas. Squamous cell carcinoma is the most common cell type in lung fibrosis. Mechanisms such as proliferation, metastasis, angiogenesis, cancer stem cells, immunology, epigenetics, and metabolism may contribute to the initiation and progression of lung cancer in IPF patients. 2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) combined with computed tomography (CT) can assist in reliably detecting cancer. Surgery, chemotherapy, and radiation may trigger exacerbations of fibrosis. The increased use of wedge resection, proton therapy, and immunotherapy may reduce the risk of exacerbations, thereby improving survival.

Keywords: Interstitial lung disease, idiopathic pulmonary fibrosis, lung cancer

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is an interstitial lung disease with an unknown etiology, poor clinical prognosis, and progressive, irreversible nature. Patients with IPF are at a higher risk of developing lung cancer compared to healthy individuals. The reported incidence of lung cancer in these patients is between 11.2 and 36 cases per 1.000 persons annually.[1] Patients with IPF, the cumulative incidence of lung cancer significantly increases, varying from 1.1% in one year, 8.7% in three years, 15.9% in five years, and reaching 31.1% in a decade of follow-up. Factors increasing the risk of lung cancer include advanced age, male sex, decreased lung function [more than a 10% decline in force vital capacity (FVC), low carbon monoxide diffusion capacity (DLCO)], and smoking.[2] The prevalence of lung cancer is 9 times higher in patients with combined pulmonary fibrosis and emphysema (CPFE). Additionally, higher rates of lung cancer are observed in IPF lung transplant recipients, suggesting shared molecular links between these two diseases.[3] The most common histological type of lung cancer in individuals with IPF is squamous cell carcinoma, followed by adenocarcinoma, which is more frequently seen in the lower lobes. Furthermore, mucinous adenocarcinoma is reported to be more common in IPF patients.[4] The 5-year survival rate for lung cancer patients with IPF is 14.5%, while it is 30.1% in those without IPF.[5]

PATHOPHYSIOLOGY

The shared molecular pathways between established lung cancer and pulmonary fibrosis include epithelial-mesenchymal transition (EMT), mesenchymal activation, and mutations in pulmonary-surfactant associated proteins (SFTP).[6] Histopathological features of IPF include fibroblast foci, subpleural fibrosis, and honeycomb structures.[7] Most lung cancer cases associated with IPF are located in areas related to IPF and have a worse prognosis.[8] The mechanical forces generated in IPF promote the initiation and progression of lung cancer. Mechanical stimulation not only directly activates the proliferation signaling pathways of local cancer cells and promotes their spread by providing a dense growth factor microenvironment, but it also supports cancer progression by awakening dormant cancer cells.[9] Mechanical disruption globally regulates the epigenetic response (chromatin accessibility, DNA methylation, and non-coding RNA), facilitating cancer progression. Mechanical forces originating from IPF lung tissue sustain angiogenesis by promoting the proliferation, differentiation, and migration of endothelial cells. Specific gene mutations, including microsatellite instability, fragile histidine triad, oncoprotein p53, and loss of heterozygosity, have been observed in many IPF cases, especially in the characteristic peripheral lung regions with honeycomb appearance.[10] Mutations affecting telomere shortening and telomerase expression are also found in familial IPF cases. Janus kinase and SFTP mutations have been found in families with both IPF and lung cancer association.[11]

The mechanical cues arising from the fibrotic response in IPF help cancer cells maintain stem cell properties. The

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mechanical environment in IPF modulates the immune microenvironment by promoting the infiltration of pro-tumorigenic macrophages, programmed death ligand 1 (PD-L1) expression, the transition from M0 to M2 macrophages, and the release of transforming growth factor-β1 (TGF-β1) from mast cells. The mechanical forces in IPF can prime premalignant cells for proliferation by activating glycolysis and providing energy to sustain proliferation and metastasis.[12] Transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF) play roles in both lung cancer and pulmonary fibrosis, with VEGF potentially promoting cell survival and proliferation through extracellular signal-regulated kinase 1/2 (ERK1/2) and phosphoinositide 3-kinase (PI3K) activation. VEGF messenger ribonucleic acid (mRNA) is elevated in endothelial progenitor cells from IPF patients.[13] TGF-β receptors lead to changes in cellular behavior, and low receptor levels promote metastasis and cancer progression, playing a crucial role in early carcinogenesis. Chronic inflammation is a common feature in both pulmonary fibrosis and tumor development.[14] The inflammatory microenvironment in the lungs includes the initiation and progression of cancer cells, excessive collagen accumulation, and other ECM components, leading to tissue remodeling. This altered lung architecture and increased stiffness can create a microenvironment supportive of cancer cell growth which may involve changes in the ECM and cytokine profiles.[6] Both in cancer and pulmonary fibrosis (particularly IPF), molecules like fascin, laminin, and heat shock protein 27, which are associated with cell migration and invasion, are expressed in bronchiolar basal cells and epithelial cells around fibroblast foci, contributing to the invasive front of tumors.[15] Furthermore, matrix metalloproteinases and integrins, known for their roles in cell invasion, are strongly linked to the development of stem cell-like properties in cancer cells and, in the context of IPF, promote the initiation, maintenance, and resolution of tissue fibrosis. Clinical trials are investigating inhibitors such as the humanized antibody STX-100 and specific antibodies against αvβ6.[16] Epithelial-to-mesenchymal transition (EMT) is a process where epithelial cells undergo changes to become more mesenchymal, and the transition of cells from an epithelial to mesenchymal phenotype can promote tissue remodeling. EMT can contribute to tissue remodeling in the lungs and create a microenvironment that supports cancer growth.[17] Circulating and cell-free deoxyribo nucleic acid (DNA) and abnormal mRNA levels are considered diagnostic and prognostic biomarkers for both cancer and IPF. The abnormal expression of specific non-coding RNAs in IPF affects genes related to fibrosis, extracellular matrix (ECM) remodeling, EMT induction, and apoptosis, potentially contributing to functional impairment in patients with lung fibrosis.[18]

DIAGNOSIS

It is important to carefully compare CT scans to identify new solitary nodules. Due to the increased risk of lung cancer in IPF, high-resolution computed tomography (HRCT) should definitely be considered in these patients. New pulmonary nodules should be evaluated further according to the high-risk group criteria of the Fleischner guidelines.[1] Additionally, mediastinal lymph node enlargement is common in interstitial lung disease (ILD) patients, which reduces the specificity of this method for detecting lung cancer.[19] For nodules larger than 8 mm, positron emission tomography and computed tomography (PET CT) should be requested. Suspicious mediastinal lymph nodes can be sampled using endobronchial ultrasound-guided transbronchial needle biopsy (EBUS-TBNB) and radial EBUS for peripheral lesions.[20] Biopsy under CT guidance should be planned for patients with neoplastic lesions suspected, and it should be remembered that the risk of complications such as pneumothorax due to the procedure may be higher. A "liquid biopsy" aimed at revealing driver mutations and determining individualized treatment for frail patients could also be considered.[11]

TREATMENT

The treatment of lung cancer in patients with fibrosis is complex: surgery, chemotherapy, and radiation can trigger exacerbations of fibrosis and increase the likelihood of poor outcomes.[21] Since patients with ILD often have impaired lung function, advanced age, and numerous comorbidities, surgical procedures pose a risk factor for increased morbidity and mortality.[22] In a study of patients with cancer stage IA, 5-year postoperative survival rates in IPF patients were reported as 61.6%, compared to 83.0% in those without IPF.[23] The extent of surgical resection is also associated with mortality.[24] Larger procedures lead to more complications, including acute exacerbations, acute lung injury/acute respiratory distress syndrome, and higher postoperative mortality. In patients where lobectomy is not recommended, segmentectomy and wedge resection show comparable survival rates.[25] Compared to wedge resection, performing lobectomy or segmentectomy had an odds ratio (OR) of 3.83, and performing pneumonectomy or lobectomy had an OR of 5.7 for acute exacerbation of interstitial lung disease (AE-ILD).[26] As less lung is compromised in wedge resection, better outcomes are predicted, as seen with wedge resection.[27]

Radiation therapy for lesions in the lungs is generally indicated for early-stage non-small cell lung cancer (NSCLC) patients who are not candidates for surgery due to poor lung function or comorbidities, R1 surgical resection cases, and locally advanced NSCLC patients combined with chemotherapy.[28] Stereotactic body radiation therapy (SBRT) is an effective, non-invasive method for early-stage NSCLC patients who are not suitable for surgical resection. A well-known side effect of radiation therapy is radiation pneumonia.[29] Pulmonary toxicity occurs in 1.5-20% of patients receiving SBRT and in 5.0-25% of patients receiving standard fractionated radiation therapy. Proton beam therapy (PBT) is a newer treatment for NSCLC patients with early-stage disease and centrally located lesions, with the major advantage of delivering less scattered radiation.[30] However, PBT is not widely available, and more research is needed to demonstrate its hypothetical effectiveness for treating lung cancer. Due to potential harmful effects, radiation therapy is not commonly used in IPF patients. According to a recent retrospective, multicenter European study, only a small percentage (12.5%) of patients diagnosed with both IPF and lung cancer received radiation therapy.[31] However, radiation therapy, especially SBRT, should be considered for carefully selected patients with both IPF and lung cancer.[32]

Percutaneous image-guided ablation, sub-lobar resection, and SBRT are techniques used to treat small tumors in early-stage NSCLC with outcomes such as radiofrequency, microwave, or cryoablation. Complications such as pneumothorax, bronchopleural fistula, and pneumonia have been reported. Due to its localized effects, this approach may be valuable in ILD patients, although data are limited.[11]

Chemotherapy plays a significant role in the treatment of locally advanced and metastatic lung cancer patients.[33] A recent meta-analysis showed that acute exacerbations following chemotherapy are more common in patients with IPF compared to those without.[34] In patients with IPF and small cell lung cancer (SCLC), acute exacerbation after first-line treatment is significantly higher in IPF patients compared to those with NSCLC (31% vs. 63%).[35] Some medications increase the risk of pneumotoxicity and AE-ILD. In patients with advanced-stage NSCLC-IPF, the combination of carboplatin and etoposide showed similar mortality benefits in stage III NSCLC-IPF patients and those without IPF.[36] Another study examining the effects of carboplatin and etoposide (or paclitaxel) in fibrotic lung cancer patients reported similar median progression-free survival but poorer overall survival in fibrotic lung cancer patients.[37] Among 684 ILD patients who received first-line chemotherapy for SCLC, the acute exacerbation rate in the context of chemotherapy was approximately 8%, with lower rates observed in nab-paclitaxel-containing regimens (5%) compared to other regimens (12%).[38] The reported ILD exacerbation rates for patients receiving docetaxel or gemcitabine were 28% and 43%, respectively, while vinorelbine was not associated with AE-ILD in a small retrospective study. Pemetrexed has shown increased toxicity in IPF patients compared to other ILD patients and significantly higher toxicity compared to patients without underlying ILD.[39]

New clinical trials are testing the efficacy of specific monoclonal antibodies and tyrosine kinase inhibitors. Targeted therapies such as epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI) or anaplastic lymphoma kinase inhibitors (ALK) have been associated with pneumotoxicity.[40] A recent meta-analysis reported male gender, smoking history, and pre-existing ILDs as risk factors for EGFR-TKI-induced ILDs. Pre-existing ILD has been associated with a sixfold increased risk of developing EGFR-TKI-induced ILD.[41,42] Further studies are needed on the use of other inhibitors for ALK, EGFR, c-ros oncogen1 (ROS1), and v-Raf murine sarcoma viral oncogene homolog B (B-RAF) in patients with pulmonary fibrosis and lung cancer.[27] A study found no acute exacerbation of pulmonary fibrosis in any patients when pirfenidone was added to immune checkpoint inhibitors or carboplatin-based chemotherapy for the treatment of NSCLC. Furthermore, nintedanib, a tyrosine kinase inhibitor, has been successfully used in combination with docetaxel for advanced-stage NSCLC treatment.[43] The anti-VEGF antibody bevacizumab has been tested in patients with ILD and lung cancer, and it was reported to prevent chemotherapy-induced AE-ILD.[44] A recent meta-analysis examining the effect of anti-VEGF treatments like nintedanib, bevacizumab, and ramucirumab on EGFR-TKI-induced ILD found that combining EGFR-TKIs with anti-VEGF agents was associated with a significant reduction in ILD incidence compared to EGFR-TKI monotherapy. Nintedanib's combination with EGFR-TKIs may have significant effects such as reducing pneumotoxicity and slowing tumor growth.[45]

PD-1 mediates the up-regulation of Interleukin-17 (IL-17) and TGF-β production by PD-1+Thelper (Th) 17 cells through signal transducer and activator of transcription 3 (STAT3), which promotes lung fibrosis, and PD-1 inhibits the diferentiation of cluster of differentiation 4 (CD4)+T cells to T regulator (Treg) cells, which promotes the production of type I collagen and inhibits myofbroblast proliferation; PD-L1 on lung fbroblasts inhibits myofbroblast proliferation by inhibiting the p53 pathway and activating the focal adhesion kinase (FAK) pathway, causing myofbroblasts to evade phagocytosis, leading to excessive proliferation of myofbroblasts, resulting in lung fbrosis. In addition, PD-L1 mediates lung fbroblast-to-myofbroblast transformation (FMT) through Smad3 and β-catenin signaling pathways, thus promoting lung fbrosis; PD-L1 upregulation on lung fbroblasts promotes fbrosis by inhibiting autophagy leading to myofbroblast proliferation and ECM deposition.[46] Immunotherapy refers to immune checkpoint inhibitors (ICIs) and includes programmed death-1(PD-1) inhibitors such as nivolumab and pembrolizumab and PD-L1 inhibitors such as atezolizumab and durvalumab. In patients with ILD and lung cancer, PD-L1 levels are similar to those without ILD, and increased tissue levels of PD-L1 are associated with better outcomes.[47] Mediastinal lymph nodes of mice treated with bleomycin showed increased size and higher PD-1 and PD-L1 mRNA levels compared to controls, while pembrolizumab weakened bleomycin-induced fibrosis. The use of combination regimens or monotherapy with immunotherapy has not been widely tested in lung cancer patients with IPF. A meta-analysis including 10 studies of NSCLC treated with ICIs showed that patients with pre-existing ILD had significantly higher (almost twice as high) overall response rates compared to those without ILD. In patients with pre-existing ILD disease control rates and progression-free survival were similar to those without ILD.[48] ICIs, while enhancing the normal immune response, may enhance the anti-tumor efects of cellular immunity, leading to an immune tolerance imbalance and immunerelated adverse events (irAEs). Studies have found that the use of ICIs in patients with ILD is associated with a higher risk of developing immune checkpoint inhibitors related pneumonitis (CIP) than that in patients without ILD.[49] Currently, no studies have directly validated the utility of PD-1/PD-L1 inhibitors on pulmonary fbrosis, and conclusive experimental evidence to support their therapeutic value is scarce. Studies have shown that ICIs in patients with IPF combined with squamous cell carcinoma, the addition of antifibrotics may prevent drug-induced pneumonia or acute exacerbation of IPF. Therefore, the study of the potential mechanism of irAEs not only contributes to the immunotherapy of tumors but also plays an important role in the treatment of IPF. Whether the combination of ICIs and antifbrotic drugs can delay the pathogenesis of IPF can be considered as a research direction.[50,51]

CONCLUSION

The presence of pulmonary fibrosis in individuals with lung cancer affects both the treatment approach and prognosis. Due to impaired lung function, treatment options may be

limited, and prognosis may be worse compared to lung cancer alone. Early diagnosis of lung cancer and more effective treatment could benefit from PET-CT screening. Sub-lobar surgical resections, immunotherapy, and proton therapy show potential. Further research is needed regarding the survival and quality of life of these patients.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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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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Adenocarcinoma of the lung mimicking interstitial lung disease

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ABSTRACT

Although benign reactive conditions can be misinterpreted as malignancies, a number of malignant lesions can in turn be mistaken for interstitial lung disease. A nonsmoking male aged 66 years who presented with multifocal dispersed, parenchymal and subpleural nodules, most of them cavitated or pseudocavitated, and that radiologically mimicked non-malignant conditions, such as pulmonary Langerhans cell histiocytosis or peribronchiolar organising pneumonia with bronchiectasis on computed tomography scan, was hospitalised. Microbiological and immunological tests were negative. Since sufficient tissue could not be obtained via bronchoscopy, the patient was scheduled for video-assisted thoracic surgery. The final diagnosis revealed invasive adenocarcinoma with a predominant lepidic pattern.

Keywords: Lung cancer, adenocarcinoma, lepidic pattern, interstitial lung diseases, mimick

INTRODUCTION

Some diseases masquerade as tuberculosis or fungal infections. More rarely, lung cancer can mimick interstitial lung diseases. Herein, we report a lepidic predominant adenocarcinoma presenting with clinical and radiological features suggestive of interstitial lung disease.

CASE

A nonsmoking male aged 66 years presented with a 3-month history of progressive dyspnoea on mild exertion. He had initially been diagnosed with bronchiectasis 4 years ago, and underwent right lower lobectomy; there was no malignancy. He denied any history of fever, haemoptysis and/or other extrapulmonary symptoms. He was hypertensive and had a history of diabetes mellitus. He had no known exposure to tuberculosis, and no history of a positive tuberculin skin test. In addition, his family medical history was unremarkable. His vital signs were within the normal range: arterial blood pressure was 120/80 mm Hg, heart rate was 80 beats per minute and transcutaneous arterial oxygen saturation was 98%, while breathing room air. General physical examination was unremarkable, and initial laboratory evaluations were all normal. The chest radiograph taken on admission revealed ill-defined parenchymal opacities in the peripheral areas of both lungs (**Figure 1**). A thorax computed tomography (CT) scan revealed bilateral, parenchymal and subpleural nodules of different shapes and sizes, surrounded by ground-glass areas (halo sign). The nodules presented with random apical-to-basilar distribution, and most showed cavitation or pseudocavitation. There were also some cystic lesions of variable wall thickness. Opacities were noted along the bronchi, and were observed in both the peripheral and central zones. No features of mass or mediastinal lymph nodes enlargement were found (**Figure 2**).

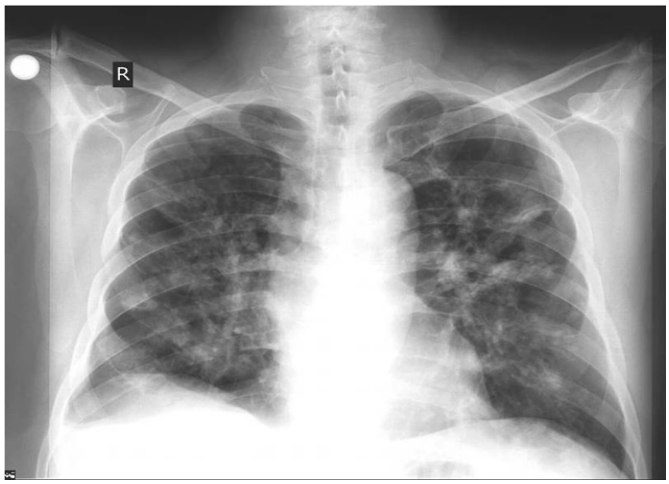

Figure 1. The chest X-ray on admission demonstrated ill-defined parenchymal opacities in the peripheral areas of both lungs

There are numerous differential diagnoses of multiple patchy and mostly cavitary nodules in the lung. The most likely diagnoses included peribronchiolar organising pneumonia, pulmonary langerhans cell histiocytosis (PLCH), granulomatosis with polyangiitis, connective tissue disease with pulmonary involvement, bronchocentric granulomatosis, tuberculosis infection with atypical

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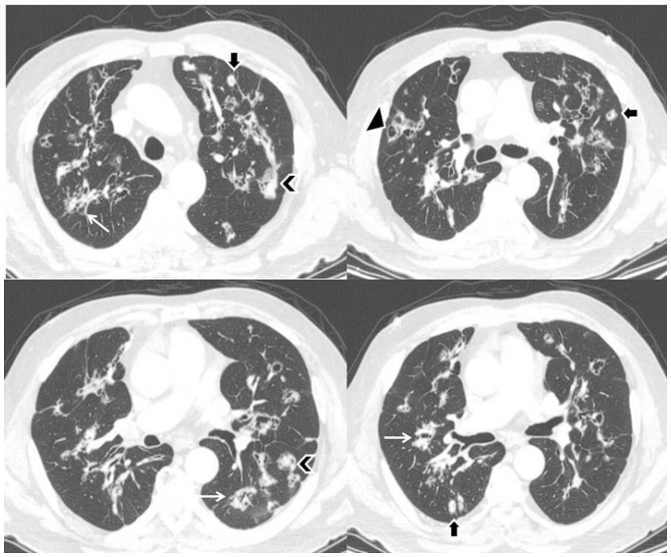

Figure 2. Thin-section computed tomography scans through different sections demonstrate radiolucencies (thin arrows) mimicking pseudocavitations, thin wall cavities (arrowheads), nodules (square brackets) surrounded by a halo of ground-glass attenuation (halo sign) and nodules with central lucency – the 'Cheerio sign' (thick arrows)

mycobacteria, pulmonary sarcoidosis, metastatic malignancies and primary carcinoma of the lung. Fiberoptic bronchoscopy was performed; no malignant cells were found in the bronchial lavage, and no specific diagnosis could be made. Transbronchial lung biopsy of the left upper lobe was also performed and was non-diagnostic. A full autoimmune screen, including antinuclear, antineutrophil cytoplasmic and double-stranded antibodies, was carried out and was negative. The patient was scheduled for video-assisted thoracic surgery with lung biopsy, and the final diagnosis revealed invasive adenocarcinoma with a predominant lepidic pattern, and positivity for thyroid transcription factor-1 (TTF-1) expression. As the next step, fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) scan imaging revealed multiple solid parenchymal and subpleural nodules, some of which were cavitated with slightly increased FDG uptake (SUVmax:3.1) (**Figure 3**). No other pathological FDG uptake was detected, and the bilateral pulmonary involvement meant that the patient was staged as T4N0M1a. The epidermal growth factor receptor (EGFR) gene and echinoderm microtubule-associated protein-like 4 (EML4) anaplastic lymphoma kinase (ALK) fusion gene were negative for mutations. The patient was instructed to follow up with an oncologist for chemotherapy.

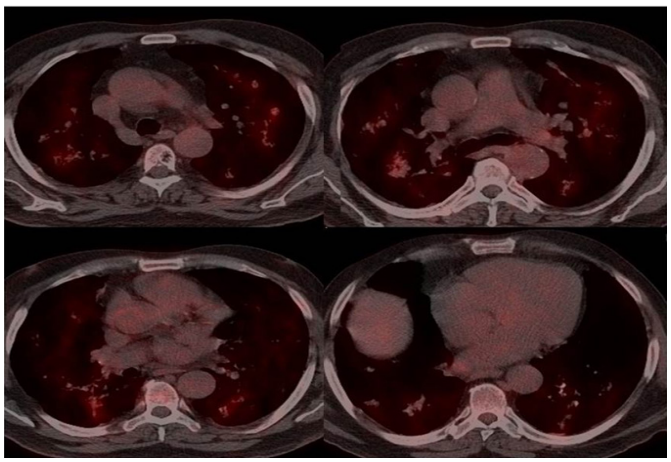

Figure 3. Fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography/computed tomography scan showing moderate uptake of FDG in the bilateral interstitial infiltrations

DISCUSSION

Adenocarcinoma has a tendency to manifest in a multifocal fashion. Over the years, many authors have documented several unique characteristics of multifocal adenocarcinomas. For example, some studies have reported a predominance in females, while others have shown a male predominance. Similarly, some studies have reported a predominance in non-smokers, while others have shown a smoker predominance.[1] Our patient was a non-smoking male.

Most patients with multifocal adenocarcinomas are asymptomatic and are incidentally diagnosed. Symptomatic patients can present with cough (28–30%), haemoptysis (6–13%), weight loss (2–6%), chest pain (6–7%) and dyspnoea (2–4%).[1] Our patient had progressive dyspnea.

The previously used classification of *bronchoalveolar carcinoma* (BAC) included a heterogenous spectrum of subtypes, but the revised classification of 2011 better reflects the pathological, radiological and clinical correlation of lung adenocarcinoma; therefore, it is more practical and useful. BAC is now categorised into the following termas: adenocarcinoma in situ, minimally invasive adenocarcinoma, lepidic predominant adenocarcinoma, predominantly invasive adenocarcinoma with some nonmucinous lepidic components and invasive mucinous adenocarcinoma. Interestingly, this group of tumours tends to be multifocal.[2]

Radiographical findings that suggest multifocal adenocarcinomas have several remarkable characteristics. These are often difficult to distinguish from non-malignant conditions and include; (a) patent intratumoural bronchioles (air bronchiologram); (b) bubble-like lucencies or pseudocavitations; (c) cavitation; (d) serpentine radiolucencies; (e) internal alveologram; and (f) multiple, thin-walled cystic lesions. Bronchioloalveolar carcinoma may have a widespread multinodular pattern, but the cavitary form is very uncommon.[3] A cavitary nodule, with a central lucency observed on CT, is reminiscent of the breakfast cereal 'Cheerios', and was first defined as 'the Cheerio sign'.[4] A Cheerio in the lung arises from proliferation of either neoplastic cells, such as adenocarcinoma, other primary lung cancers, metastases or non-malignant cells, such as PLCH, mycobacterial or fungal infections, granulomatosis with polyangiitis (formerly Wegener granulomatosis), and rheumatoid nodules.[5] All of these diseases were differential diagnoses and we sequentially excluded all of them.

Adenocarcinoma in situ, minimally invasive adenocarcinoma, invasive lepidic predominant adenocarcinoma and invasive mucinous adenocarcinoma may give rise to the Cheerio sign. The lepidic growth pattern of the tumour cells, whether solely, predominantly or partially present in these lesions, classically maintains alveolar architecture and bronchial patency, thereby creating Cheerio signs on CT at times[2,5]; some of our patient's nodules showed the Cheerio sign (**Figure 2**). Tailor et al.[6] demonstrated that pseudocavitation on CT is more common in lung adenocarcinoma than in other types of

non-small-cell lung carcinoma, with low sensitivity, but high specificity (>90%). They also showed that pseudocavitation on CT is associated with lepidic growth at histopathology. Multiple pseudocavitations were observed on our patient's CT scan (**Figure 2**).

PET scans are less sensitive, independent of tumour size, and secondary to the slow rate of proliferation of these lesions compared with other lung cancers, and are often negative.[7,8] In our case, all lesions showed slightly increased FDG uptake.

Multifocal adenocarcinomas may exhibit a lower tendency for nodal or extra-thoracic metastasis than other types of lung cancer. Although 65% of multifocal adenocarcinomas are confined to a single lobe, 12% are bilateral.[1] According to the tumour, node, metastasis (TNM) classification of lung cancer, multifocal adenocarcinoma involving more than one lobe is classified as T4, and multifocal adenocarcinoma involving the same lobe is classified as T3. The upcoming eighth edition of American joint commission on cancer (AJCC) staging for lung cancer recognises multifocal adenocarcinoma as a unique disease entity and adopts the size of the largest nodule for staging. A letter 'm' in parentheses will denote the multifocal nature of the disease.[9] The bilateral pulmonary involvement meant that our patient was staged as T4N0M1a.

The curative therapy for multifocal adenocarcinoma is surgical resection, and inappropriate patients should be directed to systemic treatment. Both cytotoxic chemotherapy and targeted therapy have a role in treating patients with advanced disease. Tissue should be tested for molecular markers (EGFR mutation and ALK rearrangement). Targeted therapy should be first-line only for patients with an EGFR mutation or the ALK fusion oncogene.[1] Liu et al.[10] analysed 78 patients with multifocal adenocarcinomas presenting as ground glass opacity for EGFR mutations in exons 18–21, and identified at least one EGFR mutation in at least one specimen in nearly 50% of patients. The authors concluded that the majority of the multifocal adenocarcinomas they investigated appeared to have arisen as independent events.

CONCLUSION

Unfortunately, molecular markers were negative in our patient, so he was scheduled to receive cytotoxic chemotherapy.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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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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Case Report

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Stevens-Johnson syndrome developed during tuberculosis treatment: a case report

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ABSTRACT

The aim of this study is to present the clinical effects and management of Stevens-Johnson syndrome (SJS), which developed during the fourth month of anti-tuberculosis treatment, specifically during the second month of maintenance treatment with isoniazid and rifampicin. This case report describes a 50-year-old male patient who developed SJS while undergoing tuberculosis treatment. The patient was treated with a combination of isoniazid and rifampicin. The clinical features, treatment adjustments, and patient outcomes are detailed. SJS developed in the fourth month of treatment, manifesting as widespread bullous erythematous lesions on the hands and feet, covering less than 10% of the body surface area. After discontinuing anti-tuberculosis treatment, the lesions improved within two days. When treatment with isoniazid and rifampicin was resumed after a 15-day drug-free period, lesions reappeared within three days, confirming the association of the syndrome with rifampicin. The treatment regimen was subsequently changed to moxifloxacin and ethambutol, resulting in complete resolution of the lesions within two days. Rifampicin-induced SJS requires prompt recognition and discontinuation of the causative drug. Healthcare providers, particularly in primary care settings, should be vigilant for cutaneous adverse reactions to anti-tuberculosis medications to ensure timely intervention and management. Further retrospective studies are needed to better understand the incidence and management of these reactions.

Keywords: Stevens-Johnson syndrome, tuberculosis, treatment, rifampicin, adverse reaction

INTRODUCTION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are immune-mediated reactions, primarily resulting from hypersensitivity reactions to drugs. These reactions are associated with T-cell-mediated apoptosis and keratinocyte damage. SJS typically affects 10-30% of the body surface area, whereas TEN involves a larger area, generally over 30% of skin loss.[1] Although the exact pathogenesis of the disease is not fully understood, it is believed to involve immunologic mechanisms, cytotoxic reactions, and delayed hypersensitivity reactions.[2] The diagnosis of SJS and TEN can be confirmed through clinical findings and biopsy. Skin rashes and mucosal lesions (oral, ocular, genital) are characteristic symptoms of these conditions. SJS and TEN are life-threatening emergencies; if not diagnosed and treated promptly, they can lead to severe health consequences. The reported average mortality rate for SJS is 1-5%, and for TEN, it is 25-35%; this rate may be higher in elderly patients and those with extensive epidermal detachment.[3] In clinically suspected cases, immediate discontinuation of the offending drugs and supportive treatments are necessary.

According to the 2024 World Health Organization data, tuberculosis (TB) incidence worldwide is reported as 134 per 100.000.[4] Thanks to the National Tuberculosis Control Program conducted in our country; the number of TB patients, which was 20.535 in 2005, decreased to 9.851 in 2022, and the disease incidence dropped from 29.4 per 100.000 to 11.4 per 100.000.[5] Although TB incidence is decreasing both in our country and globally, it is still considered a significant public health problem. Anti-tuberculosis treatment drugs can cause severe cutaneous adverse reactions (SCARs), such as SJS, TEN, and drug reaction with eosinophilia and systemic symptoms (DRESS).[6]

In this case report, the clinical effects and patient management of SJS, which developed during the fourth month of anti-tuberculosis treatment and the second month of maintenance therapy with isoniazid and rifampicin, are presented.

CASE

A 50-year-old male patient presented to a tertiary healthcare institution with a complaint of copious watery bloody sputum. A thoracic CT scan revealed limited cavitary lesions and areas of infiltration in the upper lobe of the right lung. The patient was referred to the tuberculosis dispensary for sputum AFB testing with a preliminary diagnosis of TB. A PA chest radiograph showed increased opacity in the right

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upper zone and widespread infiltration areas in both lungs. The patient was advised to wear a mask and avoid crowded places until the sputum AFB results were available. When the sputum AFB result returned positive, the patient was diagnosed with pulmonary TB and started on a four-drug initial treatment regimen (isoniazid 300 mg, rifampicin 600 mg, pyrazinamide 2000 mg, ethambutol 1500 mg). By the end of the second month, with a negative sputum AFB result, the patient transitioned to maintenance therapy (isoniazid 300 mg, rifampicin 600 mg).

In the fourth month of treatment, widespread bullous lesions accompanied by itching were observed on both hands and feet, with yellow crusts (**Figure 1**). Laboratory findings revealed: CRP: 8.6, AST: 27, ALT: 27, Direct bilirubin: 0.21, Indirect bilirubin: 0.82. The history revealed that erythematous lesions initially appeared on the plantar and dorsal surfaces of both hands and spread to the anterior surfaces of the feet and legs within 3-4 days. The lesions covered less than 10% of the body surface area. With a provisional diagnosis of drug-induced SJS, the anti-tuberculosis treatment was stopped, and the patient was referred to the dermatology clinic. The dermatology specialist prescribed oral prednisone, antihistamines, and topical steroids. Two days after discontinuing the TB treatment, the lesions resolved and dried up, and by the 10th day, they had completely healed and the patient's symptoms had subsided.

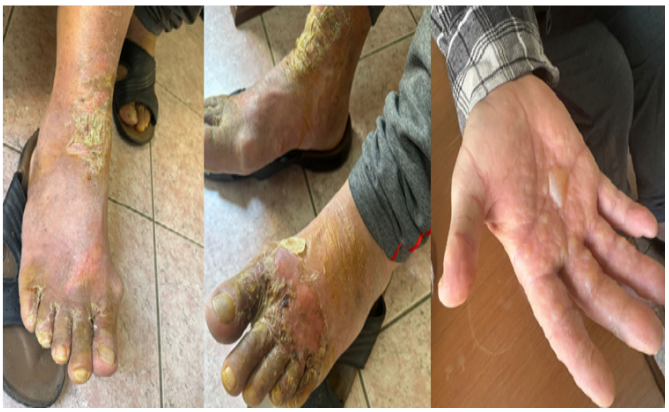

Figure 1. Lesions developed during the fourth month of anti-tuberculosis treatment

After a 15-day drug-free period, the patient was restarted on maintenance therapy with isoniazid 300 mg and rifampicin 600 mg. On the third day after resuming the medication, pruritic lesions were observed on the plantar and dorsal surfaces of both hands (**Figure 2**). The resolution of the lesions after discontinuation of anti-tuberculosis treatment and their recurrence upon reinitiation of therapy led to the conclusion that the SJS was associated with rifampicin. Isoniazid and rifampicin were discontinued, and the treatment regimen was changed to moxifloxacin 400 mg once daily and ethambutol 1500 mg once daily. Two days after the treatment adjustment, the pruritic lesions on both the plantar and dorsal surfaces of the hands completely resolved.

DISCUSSION

A retrospective study examining cutaneous lesions induced by anti-tuberculosis medications identified the most common adverse effect as rifampicin, followed by isoniazid, ethambutol, and pyrazinamide, in descending order of frequency.[6] In this case, erythematous lesions developed on both hands and feet during the fourth month of anti-tuberculosis treatment, which later spread to the anterior surfaces of the feet and legs, covering less than 10% of the body surface area, indicating SJS. The complete resolution of lesions during a 15-day drug-free period supported the preliminary diagnosis. Three days after the resumption of maintenance therapy, erythematous pruritic lesions were observed on the plantar and dorsal surfaces of both hands, confirming the diagnosis of SJS. The treatment regimen was immediately altered, resulting in the complete resolution of erythematous lesions within two days.

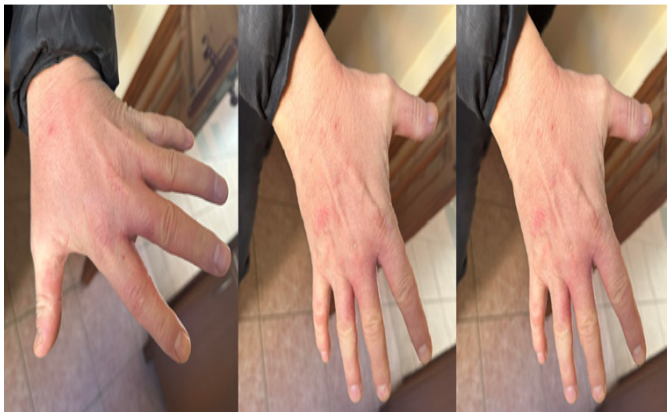

Figure 2. Lesions were observed to recur on the fourth day after resumption of treatment

CONCLUSION

Tuberculosis Dispensaries serve as the primary point of contact for patients undergoing TB treatment and play a crucial role in close follow-up and communication. Continuous communication between TB patients and healthcare workers is vital for effective TB management, which is a significant public health issue. Primary care physicians must recognize SJS, which can progress to high-mortality TEN, and promptly discontinue anti-tuberculosis treatment. Recognizing and monitoring the clinical signs and symptoms of SJS, a severe adverse reaction to anti-tuberculosis medications, is essential. There is a need for retrospective studies in this field.

ETHICAL DECLARATIONS

Informed Consent
The patient signed and free and informed consent form.

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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