Received: 23 December 2019 | Revised: 16 July 2020 | Accepted: 27 July 2020

DOI: 10.1111/crj.13238

ORIGINAL ARTICLE

WILEY

Serum biomarkers in patients with stable and exacerbated COPD-bronchiectasis overlap syndrome

Zekiye Kula Sever[1] | **Haci Ahmet Bircan**[1] | **Fevziye Burcu Sirin**[2] | **Sehnaz Evrimler**[3] | **Seda Celik**[2] | **Neslihan Merd**[3]

[1]Department of Pulmonary Medicine, Faculty of Medicine, Suleyman Demirel University, Isparta, Turkey

[2]Department of Biochemistry, Faculty of Medicine, Suleyman Demirel University, Isparta, Turkey

[3]Department of Radiology, Faculty of Medicine, Suleyman Demirel University, Isparta, Turkey

Correspondence
Haci Ahmet Bircan, Department of Pulmonary Medicine, Faculty of Medicine, Suleyman Demirel University, Isparta, Turkey.
Email: ahbircan@yahoo.com, hacibircan@sdu.edu.tr

Abstract

Introduction: Bronchiectasis (B), commonly seen in patients with chronic obstructive pulmonary disease (COPD), is associated with exacerbations and predicts mortality.

Objectives: To differentiate patient groups with COPD-(B+) or COPD-(B−) and their exacerbations by using inflammatory markers.

Methods: Consecutive COPD patients were divided into two groups according to findings on high resolution thorax CT (HRCT) images using Smith and modified Reiff scores. Patients were prospectively followed for possible future exacerbations. Serum fibrinogen, C-reactive protein (CRP), soluble urokinase-type plasminogen activator receptor (suPAR) and Plasminogen activator inhibitor-1 (PAI-1) levels were studied during exacerbation and stable periods.

Results: Eighty-seven patients were included and (85 M, 2 F), mean aged was 68.1 ± 9 (46-87). HRCT confirmed bronchiectasis in 38 (43.7%) patients, most commonly in tubular form (89.4%) and in lower lobes. COPD-B(+) group had lower body mass index ($P = 0.036$), more advanced stage of disease ($P = 0.004$) and more frequent exacerbation ($P = 0.01$). The HRCT scores were correlated with exacerbation rate ($r = 0.356$, $P < 0.05$). Fibrinogen and CRP values were higher in exacerbation ($P = 0.01$, $P = 0.013$, respectively) especially in COPD-B(+) patients. suPAR and PAI-1 levels were also higher in COPD-B(+) patients although it was not statistically significant.

Conclusion: Bronchiectasis is common and causes frequent exacerbations in COPD. Identifying of COPD-B(+) phenotype by HRCT scoring systems has considerable importance for both therapeutic options and clinical outcome of the disease. In addition to fibrinogen and CRP, high serum levels of suPAR and PAI-1 suggest us their significant roles in increased systemic inflammation associated with coexisting of COPD and bronchiectasis.

KEYWORDS

bronchiectasis, chronic obstructive pulmonary disease, C-reactive protein, exacerbation, inflammation, plasminogen activator inhibitor-1, soluble urokinase-type plasminogen activator receptor

1 | INTRODUCTION

With the increased use of CT, bronchiectasis is seen in approximately 30%-40% of COPD patients but the causes of coexistence COPD and bronchiectasis have not yet been clearly identified. The presence of bronchiectasis in COPD patients (COPD-(B+)) leads to serious deterioration in respiratory functions, increase in the number of exacerbations per year and the more detection of potential pathogenic microorganisms and a higher morbidity/mortality compared to COPD patients without bronchiectasis (COPD-(B−)).[1,2]

Structural damage in the airways, loss of epithelial cell integrity, decreased mucociliary clearance and mucus hypersecretion are accepted factors that lead to increase in mucosal damage and inflammation.[3] As a result of these tissue damage and remodeling bronchiectasis may occur. Previous studies have shown that airway inflammatory response assessed by some local biomarkers such as sputum IL-6 and IL-8 and some systemic biomarkers such as serum CRP, fibrinogen, albumin and erythrocyte sedimentation rate has been shown to be higher in COPD-(B+) patients.[4-6]

Serine proteases involved in COPD pathogenesis include neutrophil elastase, cathepsin G, proteinase 3, granzymes, plasmin, thrombin and urokinase-type plasminogen activator (uPA). The uPA which binds to the receptor on macrophage, converts plasminogen to plasmin and plasmin plays a role in cellular invasion via fibrin degradation and matrix metalloproteinase activation.[7] Various inflammatory cytokines may increase receptor (uPAR) expression.[8] Both uPAR and the soluble form of uPAR (suPAR) can bind to integrins and regulate their functions. suPAR contributes to plasminogen activation, cell adhesion, migration and proliferation, inflammation, chemotaxis, proteolysis, immune system activation, tissue remodeling, and intracellular signal transduction.[9] Various observational studies showed that suPAR was increased in cardiovascular disease, cancer and various infectious and inflammatory diseases,[9,10] suggested that it may be a risk marker and may predict prognosis in various infective diseases.[9-11]

Plasminogen activator inhibitor-1 (PAI-1) (also known as SERPIN1) is a member of the serine protease inhibitors. PAI-1 is the main inhibitor for fibrinolysis. PAI-1 plays an important role in the pathogenesis of arterial and venous thrombosis at high concentrations, and has been associated with obesity, insulin resistance, diabetes and premature aging.[12-14] All of these conditions are common in patients with COPD.[15,16] Based on these findings, we aim to identify the effect of bronchiectasis in COPD exacerbations and evaluate the predictive features of these inflammatory biomarkers to detect exacerbations in COPD-(B+) patients, since it has not been studied yet to date in patients who had these two diseases concomitantly.

2 | METHODS

2.1 | Patients

COPD was diagnosed in patients aged older than 40 years. All the COPD patients were current or ex-smokers (more than 10 packed-years).

2.2 | Pulmonary function test

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.[17]

2.3 | Definition of exacerbation or stable phases of COPD

COPD exacerbation (COPD-AE) was clinically defined according to the GOLD and the Anthonisen criteria.[15,18] COPD stable phase (COPD-S) was defined as lack of evidence of exacerbation for at least 4 weeks.

2.4 | Assessment COPD symptoms

COPD symptoms were assessed by using the Turkish version modified Medical Research Council (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 2017 multidimensional approach.[15]

2.5 | Patient recruitment

Consecutive COPD patients, stabile or exacerbated, were recruited from either outpatient or inpatient clinic in 2017-2019 years. All the patients gave their consent agreement prior to participation, were informed about the symptoms of exacerbations and followed up in the next year with clinical visits in every 3 months and with telephone visits in every month for COPD-AE.

Since suPAR and PAI-1 serum values may be influenced by some disorders, the patients who had diagnosis of lung cancer, active tuberculosis, cystic fibrosis, asthma, genetic diseases, liver cirrhosis, acute or chronic renal failure, heart failure, uncontrolled hypertension, uncontrolled diabetes mellitus comorbidities or pregnancies were excluded. Patients with sarcoidosis, histoplasmosis, systemic lupus erythematosus, Sjogren, rheumatoid arthritis, allergic bronchopulmonary aspergillosis, Crohn's disease, ulcerative colitis and active bacterial and fungal infection were excluded from the study to exclude other etiological causes of bronchiectasis. The patients who were unable to perform spirometry adequately were also excluded from the study.

This Study was supported by Scientific Research Fund of the Suleyman Demirel University (Project Number: 5026-TU1-17).

2.6 | Diagnosis and radiological evaluation of bronchiectasis

Computerized tomography (CT) scan was performed and high resolution (HRCT) images were obtained from all COPD patients when they were in stable phase of the disease. All helical CT scans were performed with Siemens Somatom Definition AS, a 128 slice CT machine. Imaging parameters were as follows; automatic effective mA, 120 kVp, gantry rotation speed 0.5 seconds, slice thickness 1 mm. Images were evaluated with Picture Archiving and Communication System (PACS), OsiriX MA v. 10.0.1 (Pixmeo), FDA approved Mac OS X radiology work station. All images were evaluated by two experienced radiologists in consensus, blinded to the clinical data. CT features which are helpful for diagnosis of bronchiectasis are, lack of bronchial tapering, bronchi visible in the peripheral 1 cm of the lungs, increased bronchoarterial ratio.[19] Normal bronchial to adjacent pulmonary arterial diameter ratio (measured from outer wall to outer wall) is approximately 1:1. This ratio increases in cases of bronchiectasis. However, the normal ratio can be measured up to 1.3:1 in some healthy people.[20] In order to be more sensitive, the bronchoarterial diameter ratio ≤1 was accepted as B(−), whereas > 1 was accepted as B(+).

In this study, we used Smith and Modified Reiff scores for determining the existence, extension and morphological type of bronchiectasis on the performed HRCT scans.[21,22] The Smith score (0-24) evaluates the number of lobes affected (6 lobes; including lingula as a separate lobe) and grades the extension of bronchiectasis as follows; 0: absence of bronchiectasis, 1: less than 25% of the bronchi, 2: 25%-49% of the bronchi, 3: 50%-74% of the bronchi, 4: more than 75% of the bronchi.[21] Modified Reiff score (0-18) also evaluates the number of lobes affected (6 lobes; including lingula) and the degree of dilatation (tubular: 1, varicose: 2, and cystic: 3).[22]

2.7 | Laboratory studies, collection and preparation of serum samples

On the first visit, demographic characteristics, history for smoking habits, occupation, lung disease, and body mass index were recorded. Routine examinations such as complete blood count (CBC), biochemical analysis, chest x-Ray and arterial blood gas analysis, pulmonary function test, sputum culture test were performed as indicated.

Venous blood samples of patients were drawn to serum separator tubes and 3.2% of sodium citrate containing coagulation tubes during both exacerbation and stable periods. Serum and plasma fraction were obtained by centrifugation at 3000 rpm for 10 minutes and stored at −80°C until the working day.

Plasma fibrinogen was measured quantitatively based on the Clauss coagulation method (ACL TOP 700, Instrumentation Laboratory Bedford, USA). Serum C-reactive protein (CRP) was measured by nephelometric method (BNTM II, Hamburg, Germany). Quantitative measurements of both serum suPAR and PAI-1 levels were performed by enzyme-linked immunosorbent assay (ELISA) (YL Biont, Shanghai, China) according to manufacturer directions. The results of measurements were expressed as in mg/dL, mg/dL, ng/L and AU/mL, respectively.

2.8 | Statistical analysis

Statistical analysis of the study was performed with SPSS 20.0 (IBM Inc, Chicago, IL, USA) program. Descriptive categorical data were given as frequency and percentage ratio and proportional scale data as mean ± SD. The suitability of continuous numerical measurements to normal distribution was tested by Kolmogorov-Smirnov test. Nonparametric test methods were used for comparisons the variables which were not distributed normally. Mann-Whitney *U* test was preferred for comparisons of two independent groups. Monte Carlo corrected chi-squared analysis method was used to test the relationships between categorical data. A Paired sample *t* test was used to compare the difference at the serum inflammatory marker levels which was measured at stable and exacerbation period of patients. In the whole study, type-1 error value was taken as 0.05 and *P* value less than 0.05 was accepted as statistically significant.

3 | RESULTS

In all, 87 consecutive patients were recruited from the Department of Pulmonary Medicine at Suleyman Demirel University Faculty of Medicine. They had a mean age of

68.1 ± 6 years, and 85 were men. The mean post-bronchodilator FEV_1 was 53.8% ± 26.8% predicted. Demographic characteristics of patients are given in Table 1. The symptom severity of COPD was presented by CAT and mMRC with a mean of 19.4 ± 9.1 and 3.24 ± 1.2, respectively. COPD patients were classified as GOLD A, B, C and D 10.3%, 23%, 3.4% and 63.2%, respectively.

Evaluation of HRCT images confirmed the presence of bronchiectasis in 38 (43.7%) patients (COPD-(B+)) with 89% (n = 34) tubular form, 8% (n = 3) cystic form and 3% (n = 1 varicose form. Most of the patients have low scores according to Smith and Modified Reiff scores (Figure 1). Multilobar involvement of bronchiectasis was found in 27 (71.1%) patients. Bronchiectasis was most commonly seen in the lower lobes of the lung (right 52.6%, left 50%). Other locations are 23.6% in the left upper lobe, 34.2% in the right upper lobe, 39.4% in the lingula, and 44.7% in the right middle lobe. We also found that Smith and Modified Reiff bronchiectasis scores were correlated with total exacerbation rates, mild exacerbations and wheezing ($r = 0.243$, $P = 0.024$ and $r = 0.328$, $P = 0.002$), ($r = 0.325$, $P = 0.002$ and $r = 0.454$ $P = 0.000$), ($r = 0.262$, $P = 0.014$ and $r = 0.338$, $P = 0.001$), respectively.

TABLE 1 Demographic characteristics of COPD patients with or without bronchiectasis at the enrollment time

	COPD-B(−) n:49	COPD-B(+) n:38	*P*
Age (years)	68.6 ± 10.1	67.2 ± 8.2	0.273
Smoking history (packed-year)	50.4 ± 33.1	50.7 ± 32.1	0.810
BMI	26.6 ± 4.6	24.4 ± 6.3	**0.036**
Previous year			
Exacerbations	2.1 ± 2.4	2.4 ± 1.9	0.201
Hospitalizations	1.5 ± 2.0	1.8 ± 1.7	0.250
ICU Admissions	2 ± 4	2.1 ± 3.2	0.350
CAT score	18.14 ± 9.6	21.05 ± 8.3	0.142
mMRC score	3.16 ± 1.21	3.34 ± 1.23	0.501
WBC (n × 10^3/μL)	10.1 ± 4.9	11.0 ± 4.9	0.226
Neutrophil (n × 10^3/μL)	7.7 ± 6.9	8.5 ± 5.1	**0.048**
Eosinophil (n/μL)	220 ± 228	254 ± 355	0.585

Abbreviations: BMI, body mass index; COPD: CAT, COPD assessment test; ICU, intensive care unit; mMRC, modified medical research council; WBC, white blood cell count, all values are given as mean ± SD. Bold indicates significant *P* values.

At the enrollment period, COPD-B(+) and COPD-B(−) groups were quite similar in terms of age, smoking, comorbidity, and history of tuberculosis, but not for body mass index (BMI), symptom scores, airflow limitations and distribution of COPD stages. We found that COPD-B (+) group has lower BMI ($P = .036$) compared to other group. BMI was also negatively correlated with airflow limitation (FEV_1% predicted) and GOLD classification of patients ($r = -0.567$, $P < 0.01$ and $r = -0.468$, $P < 0.01$), respectively.

When the patients were examined according to their stages based on airflow limitation, (39/87) 44.8% of the patients have severe/very severe (GOLD-3-4) airflow limitation. COPD-B(−) group had more severe airflow restriction (GOLD-3), whereas COPD-B(+) group had more very severe airflow restriction (GOLD-4) ($P = 0.004$) (Figure 2). According to the combined assessment system, 65.8% in COPD-(B+) group and 61.2% in COPD-(B-) group were evaluated as Group D COPD (Figure 1). Our study population generally consisted of symptomatic patients (86.2%). About 63% of all patients and 71% of the COPD-B (+) group have the highest possible score for the mMRC dyspnea score. Patients with COPD-B(+) reported more symptoms and more frequent exacerbations in the previous year compared

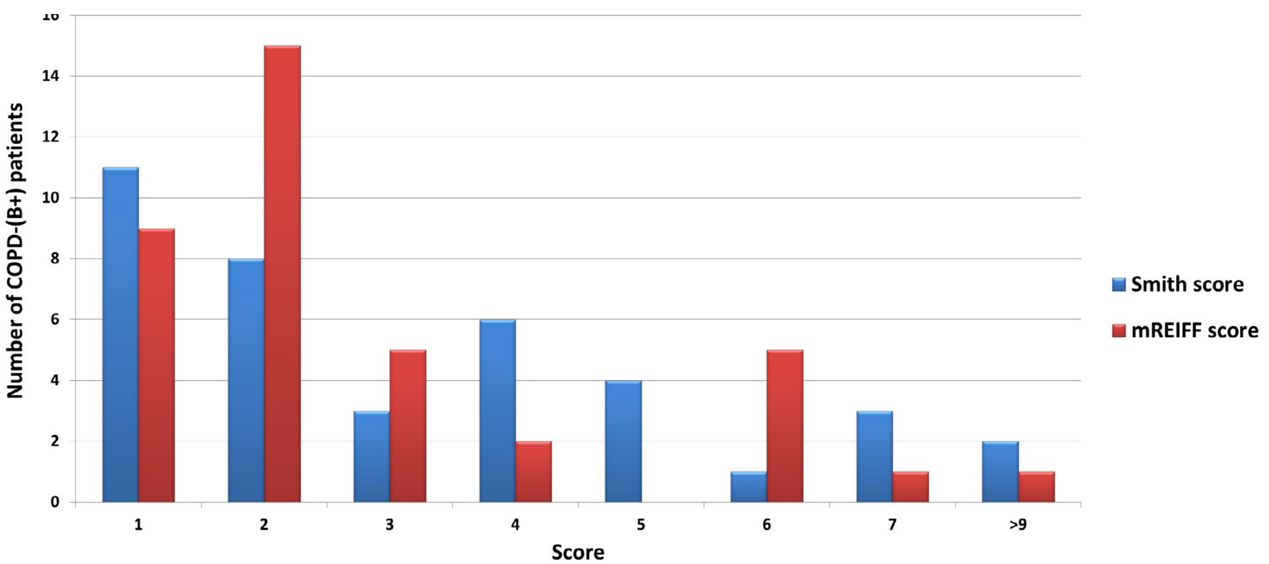

FIGURE 1 Distribution of COPD-B(+) patients according bronchiectasis scores derived from radiological evaluation [Correction added on 7 September 2020, after first online publication: Figure 1 and 2's images have been transposed.]

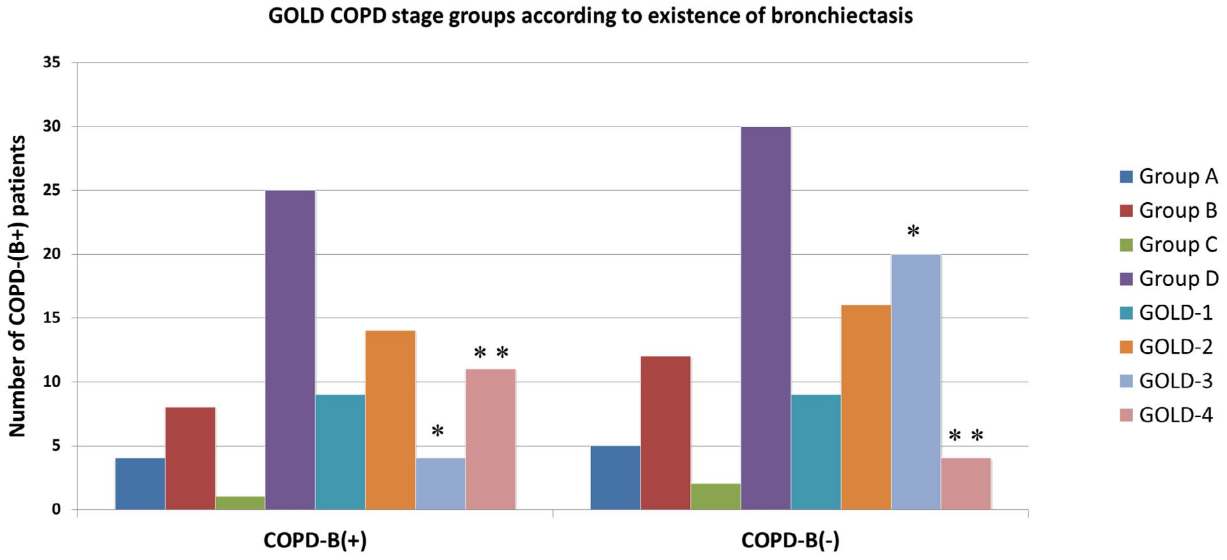

FIGURE 2 GOLD COPD stage groups according to existence of bronchiectasis

to COPD-B(−) group, although it is not statistically significant (Table 1).

All patients were followed up prospectively; mean 9.6 ± 3.3 months which including one winter season. Total exacerbation and severe exacerbations rates were higher in COPD-B(+) compared to the other group ($P = 0.01$ and $P = 0.026$, respectively). The symptoms generally found in COPD exacerbation such as increased shortness of breath, increased amount of sputum, increased respiratory rate, or tachycardia, fever, wheezing and cough during exacerbations were found significantly increased in COPD-B(+) patients (Table 2).

We also evaluate some inflammatory markers to able to differentiate each of COPD groups from others (in 73 stable and 65 exacerbated patients). It was found that serum mean CRP level were higher in exacerbated patients ($P = 0.03$) and in COPD-(B+) group ($P = 0.013$). Plasma mean fibrinogen level were higher in exacerbated patients and in COPD-(B+) group ($P = 0.01$). Serum mean suPAR level was similar in exacerbated and stable COPD patients but it was found tend to be higher in COPD-(B+) group compared to COPD-(B-) group. Serum mean PAI-1 level was higher in patients with exacerbated and in patient with bronchiectasis but the difference was not statistically significant (Table 3). We found that serum fibrinogen and serum CRP levels, but not plasma suPAR and PAI-1, showed significant correlation with Smith score ($r = 0.511$, $P = 0.003$ and $r = 0.519$, $P = 0.002$, respectively) and Modified Reiff score ($r = 0.362$, $P = 0.042$ and $r = 0.438$, $P = 0.012$, respectively), in COPD-AE patients with bronchiectasis.

4 | DISCUSSION

In the present study, we observed that COPD-(B+) group have higher inflammatory markers and more severe symptoms and airflow limitation leading to increased exacerbation rate compare to other group. In this study HRCT scan showed similar results with previous studies that bronchiectasis was mostly in tubular form (89.4%) and was a large extent in COPD-(B+) and most commonly located in the lower lobes.[23] Frequent bacterial colonization in the lower lobe airways, with chronic airway inflammation secondary to colonization, structural lung injury, longer recovery time during exacerbation, and diminished mucociliary clearance are the suggested mechanisms for predilection of bronchiectasis in lower lobes.[3,22] HRCT examination provides improved disease management in COPD patients by directly evaluation of not only pulmonary parenchyma, but also tracheobronchial system pathologies.

In this study, frequency of bronchiectasis is concordant with previous studies, ranging from 4% to 72%.[1,9,24] It has been shown that COPD-(B+) patients were older, had a low BMI and less smoked and/or active smokers.[24] In our study, low body mass index found in COPD-(B+) correlated negatively with disease stage (GOLD 1-4) and combined evaluation classification (GOLD A-D). These results may suggest us that weight loss, decreased muscle mass and decreased functional capacity may be due to systemic inflammation and it is more pronounced in COPD-(B+) patients. In accordance with previous studies, we demonstrated that COPD-(B+) patients have increased exacerbation rates and increased symptom burden related with exacerbation of disease compared to COPD-(B−) ones during the follow-up period.[5,6,23-25] In contrast to these studies, the cross-sectional study by Bafadhel et al[26] showed no relationship between bronchiectasis and exacerbation. In fact, only stable COPD patients were included and future exacerbations were not observed in that study. In another study by Jairam et al,[27] COPD patients with severe exacerbations were excluded and as a result, no association was found between exacerbations and bronchiectasis.

Our study confirmed the presence of significant correlations between HRCT scores, and increased the amount of sputum, wheezing and exacerbation frequency in patients with bronchiectasis. There are controversial reports about the relationships of bronchiectasis and exacerbation frequency. Chalmers et al[28] showed that patients with bronchiectasis who have Modified Reiff score ≥3 have increased hospital admissions, deteriorated quality of life, but the frequency of exacerbations was reported as not changed by the patients. In one study, Smith score (mean score of 5) was correlated with dyspnea severity, and decreasing at FEV_1 and PaO_2,[21] but in another it has no association with stable respiratory symptoms, spirometric measurements and exacerbation frequency.[5]

When the role of inflammatory markers are considered, an increased serum CRP level was found, whereas fibrinogen, suPAR and PAI-1 levels were not significantly changed at exacerbation period in all COPD patients. In accordance with our study, high CRP levels at acute exacerbation and pneumonia in patients with COPD were reported previously.[29,30]

There are few studies in the literature investigating the role of suPAR and PAI-1 in the pathogenesis of COPD.[31-38] In stable COPD patients, Wang et al[31] found that serum PAI-1 levels were significantly higher and suPAR levels were similar compared to healthy people. In the same study, PAI-1 was found to be negatively correlated with FEV_1/FVC and positively correlated with serum CRP and serum Metalloproteinase-1 Tissue Inhibitor (TIMP-1). In a study by Waschki et al,[32] PAI-1 serum levels were found to be higher in COPD patients than healthy people, higher in patients with moderate/severe airflow limitation, and correlated positively with triglyceride and CRP levels. In stable phase of COPD, serum suPAR level is higher than in asthma and healthy controls[33,34] and PAI-1 negatively correlated with pulmonary function.[33] To et al[35] showed that the mean PAI-1 level in COPD sputum was higher than that of both age-matched smokers without COPD and healthy nonsmokers and conclude that oxidative stress, directly or indirectly via HDAC

TABLE 2 Exacerbation characteristics of COPD patients with or without bronchiectasis in the follow-up period

	COPD-B(−) n:49	COPD-B(+) n:38	*P*
Total exacerbation	1.6 ± 1.3	3.3 ± 2.4	**0.01**
Serious exacerbation	0.5 ± 0.7	1.2 ± 1.4	**0.026**
Moderate exacerbation	0.6 ± 0.9	1.1 ± 1.3	0.087
Mild exacerbation	0.4 ± 0.5	0.9 ± 1.2	**0.037**
Increased dyspnea	1.4 ± 1.2	3.1 ± 2.4	**0.001**
Increased amount of sputum	0.9 ± 0.9	1.8 ± 1.7	**0.009**
Increased purulence of sputum	1.1 ± 1.1	1.9 ± 1.9	0.086
Upper respiratory tract infection	0.2 ± 0.5	0.4 ± 0.6	0.292
Fever	0.1 ± 0.3	0.5 ± 0.7	**0.011**
Wheezing	0.3 ± 0.6	0.9 ± 1.2	**0.017**
Cough	0.8 ± 0.9	1.2 ± 1.0	**0.022**
Tachypnea	0.1 ± 0.4	0.5 ± 0.7	**0.003**
Tachycardia	0.08 ± 0.2	0.3 ± 0.5	**0.005**

Note: The values represent the mean ± SD value of the each exacerbation symptom experienced. Bold indicates significant *P* values.

TABLE 3 Mean serum levels of inflammatory biomarkers in COPD patients according to presence of bronchiectasis in both stable and exacerbation period

Biomarker	Period	All patients†	COPD-B(−) n:49	COPD-B(+) n:38	*P*
Fibrinojen	Stable	364.8 ± 155.3	365.4 ± 162.5	361.3 ± 149.9	0.868
	Exacerbation	422.7 ± 195.6	354.9 ± 115.6	486.2 ± 232.8	**0.01**
CRP	Stable	10.5 ± 18.1*	11.7 ± 21.3	9.2 ± 13.8	0.342
	Exacerbation	36.5 ± 52.9*	17.3 ± 29.6	51.2 ± 60.9	**0.013**
suPAR	Stable	1711.5 ± 866.4	1580.2 ± 419.9	1917.8 ± 1207	0.129
	Exacerbation	1668.9 ± 806.3	1491.9 ± 429.6	1832.3 ± 1053.2	0.254
PAI-1	Stable	7.2 ± 4.9	6.5 ± 2.8	8.1 ± 6.7	0.348
	Exacerbation	10.7 ± 14.1	9 ± 12.9	10.5 ± 13.6	0.094

Abbreviations: CRP, C-reactive protein; PAI-1, plasminogen activator inhibitor-1; suPAR, soluble urokinase-type plasminogen activator receptor.

* $P = 0.006$, paired sample test COPD-S versus COPD-AE.

† 74 patients with COPD-S and 65 patients with COPD-AE.

Bold indicates significant *P* values.

reduction, plays a role in PAI-1 expression in COPD via activation of NF-κB.

Among the studies performed in exacerbation period, Gümüş et al[36] showed that fibrinogen, CRP and suPAR levels were significantly higher in COPD exacerbated patients compare to healthy controls, and a negative correlation between suPAR and FEV_1. In a similar study by AboEl-Magd et al[37] showed higher serum suPAR level in patients with COPD exacerbation compared to healthy group, and decreasing suPAR levels after effective treatment for exacerbation. The study done by Godtfredsen NS et al supports the value of suPAR as a marker of poor prognosis, showing that increasing suPAR levels independently predicts the 30-day mortality in a large group of acutely admitted patients with COPD.[38]

Our results about suPAR and PAI-1 do not support the studies mentioned previously. Our study has some methodological differences from the others. First, in our study, the stable period was determined as the period in which no exacerbation symptoms were observed 4 weeks before the last control or discharging from hospital. That's why the serum samples indicating stable term were not taken during or next to exacerbation treatment. Second, all severity types of COPD exacerbations were included in our study, whereas only COPD exacerbations due to bacterial infections have been included in other studies.

In the literature, several studies found increased inflammatory markers such as CRP, fibrinogen or erythrocyte sedimentation rate in COPD-(B+) patients even if in the stable period indicating that systemic inflammation is more severe in bronchiectasis group.[5,6] Our findings supported that, as the Smith and Modified Reiff scores increased, fibrinogen and CRP values increased during exacerbation period. This suggests that systemic inflammation is more severe as the severity of bronchiectasis increases. In our study, although stable and exacerbated suPAR and PAI-1 values were higher in COPD patients with bronchiectasis, no statistically significant difference was found. In the literature, there are no studies investigating suPAR and PAI-1 values in patients with bronchiectasis and COPD, and it is thought that prospective studies with larger patient groups and longer clinical follow-up are needed.

There are some limitations to the present study. First, the study was carried out at a single center with a relatively small group. The fact that our center is a tertiary referral university hospital may cause special referrals of patients such as difficult to treat, who have severe exacerbation risk and who are in the advanced stage of disease. Second, we did not compare the results of biomarkers we studied in COPD patients with a healthy control group. But our study protocol already consisted of internal control groups.

As a conclusion, bronchiectasis coexistence is common in COPD patients and causes frequent exacerbations of the disease. In addition to fibrinogen and CRP, suPAR and PAI-1 may play important roles in increased systemic inflammation associated with COPD bronchiectasis. Large scale long-term prospective studies are needed about the roles of suPAR, PAI-1 in the inflammation of COPD patients with or without bronchiectasis.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

AUTHOR CONTRIBUTIONS

ZKS: performed enrollment and follow-up of the patients, dataentry and participated writing the manuscript
HAB: formulated the hypothesis, data analysis, wrote and reviewed the manuscript
BS and SC: performed biochemical analysis, participated data entry
SE and NM: performed radiological evaluations, participated data entry.
All authors read and approved the final manuscript.

ETHICS

This study was approved by the local research ethics committee on Human Right Related to Research Involving Human Subjects, Suleyman Demirel University Faculty of Medicine.

ORCID

Haci Ahmet Bircan https://orcid.org/0000-0001-8937-3679

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How to cite this article: Sever ZK, Bircan HA, Sirin FB, Evrimler S, Celik S, Merd N. Serum biomarkers in patients with stable and exacerbated COPD-bronchiectasis overlap syndrome. *Clin Respir J*. 2020;14:1032–1039. https://doi.org/10.1111/crj.13238