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Research Article

The Co-existing of Bronchiectasis and Chronic Obstructive Pulmonary Disease: Analysis of Clinical, Radiological and Microbiological Data

Alizaman Sadigov[1]*, Ibrahim Isayev[1], Aydin Aliyev[2], Naila Mamayeva[3]

[1]Department of Pulmonary Medicine, Azerbaijan Medical University, Baku, Azerbaijan

[2]Department of Radiolog, Azerbaijan Medical University, Baku, Azerbaijan

[3]Department of Clinical and Bacteriological Laboratory; Therapeutic and Education Hospital; Azerbaijan Medical University, Baku, Azerbaijan.

***Corresponding Author**: Alizaman Sadigov, Department of Pulmonary Medicine, Azerbaijan Medical University, Baku, Azerbaijan.

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Abstract

Background: Bronchiectasis revealed by chest tomography is prevalent in patients with chronic obstructive pulmonary disease (COPD) and complex assessment of clinical, radiological and microbiological features of this comorbidity may help clinicians predict the prognosis and outcomes of the severe disease. Understanding the presence of bronchiectasis in COPD is important for future intervention and preventing disease progression.

Objective: The aim of this study was to assess the clinical characteristics, radiographic features and microbiological data and its impact to the prognostic value of bronchiectasis in patients with COPD.

Methods: Data from patients diagnosed with COPD at the Pulmonary Medicine Department of University Hospital between October 2011 and November 2016 were retrospectively collected and analyzed. SPSS statistical software was used to analyze the data. Data from 524 patients with COPD were analyzed.

Results: Bronchiectasis was evaluated in 167 patients. The presence of bronchiectasis in COPD patients was associated with more frequent disease exacerbation compared with patients without bronchiectasis ($P < 0.05$). In patients group with comorbid condition frequent exacerbation of the disease lead the more rapidly decline of lung function (FEV1) compared with patients without bronchiectasis ($P < 0.02$). The isolation of *Pseudomonas aeruginosa* (PA) from sputum was the variable most significantly associated with the presence of bronchiectasis in patients with COPD (hazard ratio (HR), 2.81; 95% confidence interval (CI), 1.28 - 5.24; $P = 0.008$). During follow-up there were 72 deaths, of which 43 were in the bronchiectasis group. The presence of bronchiectasis (HR, 1.69; 95% CI, 1.04 - 3.09; $P = 0.034$) was associated with an increase in all-cause mortality in patients with COPD.

Conclusions: The presence of bronchiectasis in patients with COPD was associated with exacerbation frequency. Frequent exacerbations of disease lead to the more rapidly decline of the lung function and disease progression. Isolation of potentially pathogenic microorganisms was more frequent in coexisting disease and the presence of *Pseudomonas aeruginosa* infection was associated with increasing of mortality among patients with comorbidity.

Keywords: *Bronchiectasis; Chronic Obstructive Pulmonary Disease; Pseudomonas aeruginosa*

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality around the word [1]. It is a complex and heterogeneous disease; the pathological and structural abnormalities, and clinical features vary greatly among patients

despite having a similar lung function [2,3]. Identifying patients groups with unique specific characteristics and clinical consequences is needed to guide therapy and management of COPD, especially for those at high risk for exacerbation and mortality, in whom a specific intervention could be tested [4].

Thoracic computed tomography is currently a non-invasive imaging tool that holds promise for phenotyping in COPD, as it reveals significant differences in morphological changes in the lungs even with similar degree of airflow limitation [5]. Underlying structural changes in COPD, such as bronchiectasis may also modulate exacerbation severity and contribute to morbidity associated with exacerbations [6]. Bronchiectasis in clinical presentations and pathophysiology such as chronic cough, sputum production, susceptibility to recurrent exacerbations and incompletely reversible airflow obstruction [7].

Several studies [8-10] have revealed an association between bronchiectasis and COPD, reporting the presence of bronchiectasis in patients with COPD is associated with increased bronchial inflammation, frequent colonization of airway by potentially pathogenic microorganisms (PPM_s) and severe airflow obstruction.

Given the potentially important impact of co-existent bronchiectasis on COPD outcomes, we investigated the clinical, radiological and microbiological data in patients with COPD associated with non-cystic fibrosis (non-CF) bronchiectasis.

Methodology

Study subjects: The study retrospectively collected the data from 524 consecutive inpatient diagnosed with COPD between October 2011and November 2016 in the Pulmonary Medicine Department of the University Hospital. Patients who had not received a chest HRCT scan examination were excluded. Clinical physicians who were involved in the study collected all of the data. Written informed consent was obtained from all of the patients. All aspects of the study were performed in accordance with relevant guidelines and regulations.

Diagnosis of COPD and non-CF Bronchiectasis: COPD was diagnosed as the presence of a post-bronchodilator forced expiratory volume in 1 second forced vital capacity (FEV1/FVC) < 70%: in patients with a long smoking history according to the criteria published by the Global Initiative for Chronic Obstructive Lung Disease (COLD) [11]. An exacerbation of COPD is a curve event characterized by a worsening of the patients respiratory symptoms that is beyond normal day-to-day variations and that leads to a change in medication [12-15].

A chest HRCT seam was used to coin form the diagnosis of bronchiectasis. High-resolution images were obtained in full inspiration at 1 mm collimation and 10 mm intervals from the apex to the base of the lungs. The type of bronchiectasis was defined according to the morphology of bronchiectasis. Cases of small bronchiectasis only visible in a single pulmonary segment were ignored, because this sign can appear in a large proportion of the healthy population [16].

Interview Questionnaire and Blood Samples: A standardized protocol was used for obtaining informed questions on the following topics: general and anthropometric information (i.e., age, sex, and body mass index); smoking history; and history of respiratory illness (i.e., nasosinusitis, tuberculosis (TB), and pneumonia) and clinical manifestation (e.g., the onset of symptoms, the property of chronic expectoration, the presence of wheezing, etc.). In addition, C-reactive protein (CRP) level, and interleukin-6 (IL-6), concentrations in the blood were used as markers of systemic inflammation and albumin level was used as a marker of nutritional status. Oxygen and carbon dioxide partial pressures (PO_2 and PCO_2, respectively) and the acidity of the blood (pH) were also assessed. The detailed study procedure is shown in figure 1.

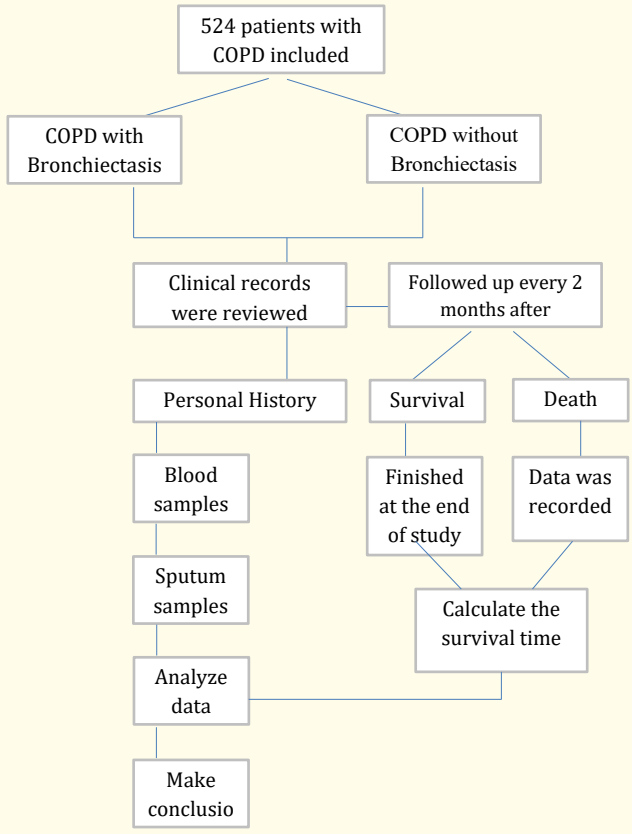

Figure 1: *The detailed study procedure to ensure that all of the researchers performed their assignments according to protocol.*

Sputum Samples: The microbiologic analysis of daily spontaneous morning sputum was requested for each patient during hospitalization. Patients were taught how to correctly collect sputum samples using the most sterile technique possible, and they were asked to deposit the samples at the hospital laboratory within a maximum of 2h after collection. Sputum samples were accepted if they contained fewer than 10 squamous epithelial cells and more than 25 leucocytes per low-powered field. Sputum cultures were expressed as colony-forming units (CFUs) per ml. A cutoff point of 103 CFUs/ml or more was defined as significant for the identification of abnormal positive culture results for PPM [17-19]. Isolated bacterial agents were classified into PPM strains, including PA, *Klebsiella pneumonia, Escherichia coli, Baumannii, Enterobacter cloacae, Aspergillus* and other pathogenic microorganisms.

Survival Analysis: In our department, all of the patients with COPD were routinely to sign a consent form when they were admitted to the hospital. Patients signed the consent form to authorize follow-up every 2 months through telephone or face-to-face interviews. The follow-up was completed on January 31, 2017. A patient was considered lost to follow-up if we were unable to contact him/her at each follow-up session during the study period. The end point of this study was all-cause mortality. Information regarding the cause and date of death was obtained from hospital medical records if the patient died in the hospital or from official death certificates in other situations.

Statistics: The patients were divided into the following two groups: patients who had bronchiectasis and patients who did not had bronchiectasis. Depending on whether variables were normally or non-normally distributed, either a Spearman or a Pearson coefficient

was calculated to assess the correlation between variables. A logistic regression model was used to determine the factors that were independently associated with the presence of bronchiectasis. A cox proportional hazard regression model was used to assess the factors associated with survival. The variables that presented statistically significant differences ($P < 0.05$) in the bivariate analysis and were of clinical interest were included as the independent variables in the first model. Bronchiectasis and all-cause mortality were dependent variables. Survival curves for the two groups (i.e. COPD patients with and without bronchiectasis) were constructed according to the Kaplan Meier method and were compared using the log-rank test. HR and 95%. CI for the independent variables were also calculated. $P \leq 0.05$ was considered to be significant.

Results

A total 524 patients (mean age 64.2 [8.9]; 89.4% men) with COPD were included in the final analysis after twenty one patients who did not have HRCT scans. Non-CF Bronchiectasis was present in 167 (31.9%) patients. Fourteen patients presented a history of nasosinusitis (2.7%), 98 patients presented a history of tuberculosis (18.7%) and twenty eight patients presented a history of at least one pneumonia episode (5.3%). No other conditions that can trigger bronchiectasis were found in our patients (e. g., α1 – antitrypsin deficiency, significant immunodeficiencies, systemic diseases, high-risk professions). An average of three valid sputum samples were collected from patients who had daily sputum production during the study. The most frequently isolated PPM in the entire patient population was *Pseudomonas aeruginosa* (72 patients), 60 of whom had bronchiectasis. *Escherichia coli* was isolated in 41 patients and 34 of who, had non-CF bronchiectasis, *Klebsiella pneumonia* was detected in 18 patients (3.4%), and only 3 of whom had bronchiectasis, *Acinetobacter Baumannii* was isolated in 11 patients, and in 7 patients of whom had bronchiectasis. *Aspergillus fumigatus* was isolated in 28 patients, 11 patients of whom with bronchiectasis. Non-tuberculosis mycobacteria (NTM) was evaluated in 7 patients.

The differential characteristics of the group with bronchiectasis (n = 167) and the group without bronchiectasis (n = 357) are shown in table 1 and table 2. Patients with COPD and bronchiectasis tended to be older and male, and they had a longer duration of symptoms, more purulent sputum expectoration, greater systemic inflammation, poorer nutritional status, a longer of hospitalization, more positive cultures PPMs, and more often intensive care unit (ICV) admission.

Parameter	All Patients	COPD with Bronchiectasis	COPD without Bronchiectasis	P
Subjects, N (%)	524	167 (31.9%)	357 (68.1%)	-
Sex, MIF, No	468/56	130/37	328/29	< 0.001
Age, g	64.8 (8.9)	66.9 (9.1)	63.4 (8.5)	< 0.021
Smoking index, Pack-year	64.8 (16.5)	63.7 (14.8)	66.2 (18.4)	< 0.621
Body mass index, Kg/m^2	22.7 (4.1)	21.1 (3.4)	22.8 (4.2)	< 0.05
Outset of symptoms, y	11.7 (5.7)	14.1 (5.2)	9.8 (6.4)	< 0.001
Daily sputum production, No (%)	420 (80.1%)	140 (83.8%)	280 (53.4%)	< 0.01
Purulent sputum, No (%)	285 (54.4%)	103 (61.7%)	182 (51.0%)	< 0.003
Wheezing, No (%)	482 (92.0%)	158 (94.6%)	324 (91.0%)	0.19
Previous nasosinusitis, No (%)	14 (2.7%)	10 (6.0%)	4 (1.1%)	< 0.01
Previous pneumonia, No (%)	28 (5.4%)	9 (5.4%)	19 (5.3%)	0.315
Previous tuberculosis, No (%)	98 (18.7%)	59 (35.3%)	39 (10.9%)	< 0.001
CRP, mg/L	58 (34.8)	72 (36.9)	38 (28.4)	0.0001
IL-6, pg/ml	59 (19.7)	74 (20.5)	46 (21.2)	0.001
Albumin, mg/dl	32 (5.4)	30 (5.1)	34 (4.9)	< 0.05
PO_2, mm Hg	64.7 (18.7)	61.8 (17.5)	67.1 (19.4)	< 0.001
PCO_2	46 (9.3)	50 (9.4)	42 (10.2)	< 0.001
Hypercapnia, No (%)	204 (38.9)	95 (56.9)	109 (30.5)	< 0.003
Length of hospitalization, d	12.8 (6.4)	15 (5.9)	10.9 (6.55)	< 0.001
ICU admission, No (%)	96 (18.3)	59 (35.3)	37 (10.4)	< 0.001

Table 1: *Baseline and clinical characteristics of subjects with COPD, with and without bronchiectasis, Data are presented as n (%) or mean ±SD unless otherwise stated. CRP: C – reactive protein; IL-6: Interleukin-6.*

Parameter	All Patients	COPD with Bronchiectasis	COPD without Bronchiectasis	P
Subjects, No (%)	524 (100%)	167 (31.9)	357 (68.1)	-
Patients with at least One PPM isolate, No (%)	285 (54.4)	114 (68.2)	171 (47.9)	0.005
Bacteriologic. No (%)	151 (28.8)	90 (53.9)	61 (17.0)	0.001
Pseudomonas aeruginosa isolates, No (%)	72 (13.7)	40 (24.0)	32 (9.0)	< 0.002
Escherichia coli isolates, No (%)	41 (7.8)	34 (20.4)	7 (1.9)	0.0005
Klebsiella pneumonia isolates, No (%)	18 (3.4)	3 (1.8)	15 (4.2)	< 0.002
Baumoni isolates, No (%)	11 (2.1)	7 (4.2)	4 (1.1)	< 0.002
Enterobacteriae isolates, No (%)	9 (1.7)	6 (3.6)	3 (1.0%)	< 0.004
NTM detected, No (%)	7 (1.3)	2 (1.2)	5 (1.4)	0.765
Aspergillus isolates, No (%)	28 (5.3%)	11 (6.6)	17 (3.2)	0.04

Table 2: *Microbiological characteristics of subjects with COPD, with and without bronchiectasis. NTM: Non-Tuberculosis Mycobacteria; PPM: Potentially Pathogenic Microorganisms.*

The presence of non-CF-bronchiectasis has been impact to the radiological features of comorbidity.

Parameter	Radiological Features of Patients							P
	Emphysema			Bronchial wall thickening	Type of Bronchiectasis			
	Pan lobular	Cent lobular	Par septal		Tubular	Cystic	Mixed	
Subjects, No (%)	224 (40.8)	285 (54.4)	15 (2.7)	421 (80.3)	109 (65.3)	39 (3.3)	19 (11.2)	
Sex: M/F, No	204/20	256/29	916	368/53	82/27	32/7	16/3	0.004
Age, y	64.1 (9.0)	64.2 (8.4)	65.4 (8.5)	65.7 (8.7)	64.3 (8.8)	64.3 (9.1)	65.1 (9.4)	0.215
PO_2, mm Hg	67.8 (18.5)	65.5 (17.3)	68.9 (19.2)	64.3 (18.6)	67.1 (17.8)	59.5 (18.4)	60.7 (19.4)	0.003
Albumin, ms/dd	32.1 (4.8)	34.2 (4.6)	34.7 (5.0)	34.4 (4.6)	32 (4.9)	30.1 (5.2)	31.3 (4.7)	<0.05
CRP, mg/L	39.5 (28.4)	40.4 (34.2)	34.1 (26.5)	38.9 (29.7)	68 (26.4)	74 (34.5)	70 (28.4)	0.001
IL-6, pg/ml	46.5 (19.4)	48.1 (20.4)	42.6 (17.9)	47.9 (21.6)	69 (20.3)	73 (18.4)	71 (21.5)	0.001
Length of hospitalization, d	10.4 (4.1)	12.1 (5.0)	10.1 (4.3)	10.9 (5.2)	13.4 (4.7)	16.1 (5.2)	15.7 (4.9)	0.005
ICU, admission, No (%)	37 (16.5)	56 (19.6)	2 (13.3)	79 (18.8)	22 (20.2)	26 (66.7)	11 (57.9)	0.0001

Table 3: *In patients with COPD associated with bronchiectasis common finding was multi-lobe localization of bronchiectasis and more common type of bronchiectasis was tubular bronchiectasis.*

Multi-lobe localization of bronchiectasis was higher in patients with COPD with bronchiectasis. In 103 (61.6%) of 167 patients with COPD associated with bronchiectasis was found multi-lobe (two or more) localization of bronchiectasis of the patients, 109 (65.3%) had tubular bronchiectasis. Among patients with tubular bronchiectasis respiratory failure was less than among patients with cystic or mixed types of bronchiectasis (P = 0.003). The severity of dyspnea in patients with tubular bronchiectasis was moderate compared with that in patients with cystic or mixed bronchiectasis. However, there was no significant difference in the severity of dyspnea between patients with cystic bronchiectasis and patients with mixed bronchiectasis (P = 0.615).

Exacerbation rate of patients with COPD with bronchiectasis was higher compared with that in patients with patients COPD without bronchiectasis (Figure 2).

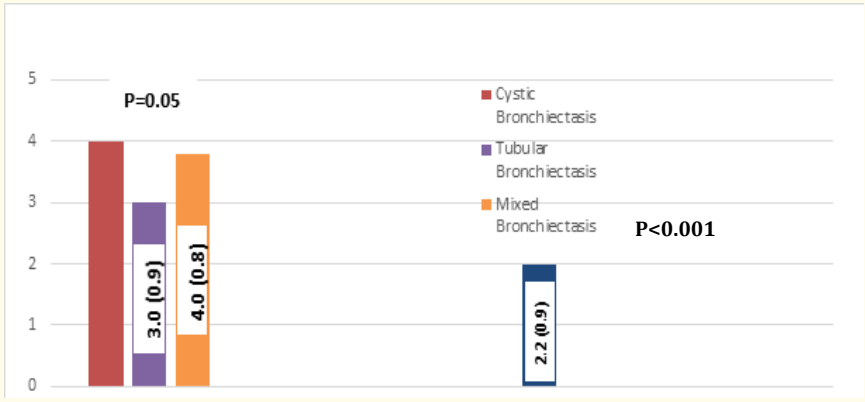

Figure 2: *Exacerbation rate differences between patients with COPD, with bronchiectasis and without bronchiectasis. Data is presented as men ± SD unless otherwise stated.*

In patients with frequent exacerbations lead to disease progression and more rapidly decline of lung function (Figure 3).

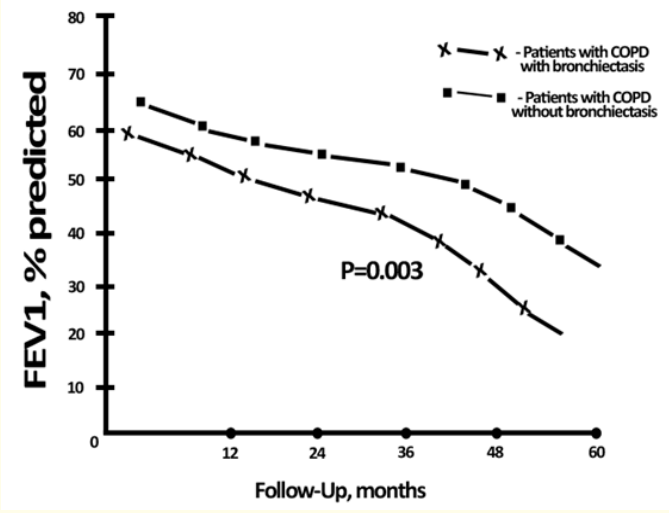

Figure 3: *Lung Function decline of patients with COPD, with and without bronchiectasis. Data is presented as mean ± SD unless otherwise stated. FEV1: Forced expiratory volume in one second.*

Frequent exacerbations of disease were associated with increasing of mortality risk of patients with comorbidity. The differential characteristics of the group who survived follow-up (n = 452) and the group who died (n = 72) are shown in table 4. The patients with COPD who died were older and presented with a longer duration of symptoms, a higher prevalence of bronchiectasis, a greater number of positive cultures of PPM, a lower peripheral albumin concentration, higher concentration of CRP and IL-G. Among patients with COPD who died the number of ICU admission was greater compared with that in patients who survived.

	All Patients	Died	Survived	P
Subjects, n	524	72	452	
Age, y	64.2 (8.9)	70.4 (8.7)	63.1 (8.6)	< 0.002
Sex, MIF, No	468/56	61/11	407/45	0.845
Onset of symptoms, y	11.7 (5.7)	15.2 (5.1)	9.8 (5.6)	0.005
Pack-years smoked	64.8 (16.5)	66.5 (18.7)	63.5 (20.4)	0.219
CRP, mg/L	58 (34.8)	84 (32.8)	38 (28.9)	0.001
IL-G, pg/ml	59 (19.7)	81 (21.4)	40 (22.5)	0.001
Albumin, mg/dl	32 (5.4)	28 (5.2)	35.7 (4.3)	< 0.03
Length of hospitalization, d	12.8 (6.4)	16.1 (4.7)	10.9 (6.2)	0.001
Isolation of PPM, No (%)	285 (54.4%)	58 (80.5%)	227 (50.2%)	< 0.001
ICU admission, No (%)	96 (18.3%)	65 (90.2%)	31 (6.9%)	< 0.0001

Table 4: *Baseline and clinical characteristics of patients according to their vital status at the end of study. Data are presented as n(%) or mean +_SD unless otherwise stated.*

Discussion

Our results shown that the isolation of PA in sputum, purulent sputum production and longer time since the onset of symptoms were independently associated with bronchiectasis. Our other finding was several factors in addition to those already known to be associated with an increased risk of all-causes mortality in patients with COPD, such as increased the exacerbations rate, decreased pulmonary function and the subsequent complication, such as respiratory failure related intensive care unit admission. Specifically, the presence of bronchiectasis, the isolation of PPM and the patient's age were associated with an increased risk in all-cause mortality in patients with COPD.

Exacerbations of COPD are important events in the course of the disease because they have a negative impact on a patient's quality of life, accelerate lung function decline, and are associated with morbidity and mortality [1,2]. The reasons why the presence of bronchiectasis in COPD can be related to more frequent and longer duration of exacerbations are speculative. Recurrent COPD exacerbations are associated with the presence of heightened airway bacterial and inflammatory burden [14,16]. The presence of bacteria in the lower airways in COPD impairs host defense mechanisms, which results in epithelial cell integrity disruption and inflammation, further airway structural damage, which could be the mechanism for longer and more severe COPD exacerbations [19]. Incomplete resolution of bacterial colonization was considered to be a risk for relapse, and therefore appropriate and effective antibiotic therapy for bacterial infection in exacerbation of COPD with bronchiectasis may be important in preventing exacerbations and relapse or delaying subsequent exacerbations [6,22,23].

The association between the presence of bronchiectasis and COPD mortality is a remarkable finding of our study. This could be explained by the potential impact of bronchiectasis on COPD. Firstly, the presence of bronchiectasis is associated with an increased risk for exacerbations. It is well known the exacerbations accelerate the rate of decline of lung function and are associated with significant mortality. Secondly, bronchiectasis is associated with severe airflow obstruction, which is also a risk for COPD death [8,12]. Thirdly, bronchiectasis is associated with systemic and pulmonary inflammation, which may be the mechanistic link between COPD and comorbid conditions, such as cardiovascular diseases, lung cancer and others, which are also contributors to mortality [10].

The prevalence of bronchiectasis in patients with COPD in our study was 31.9% of these patients, 65.3% had tubular bronchiectasis. These findings are similar to the percentages reported in previous study [20]. A deficiency in host defense combined with bacterial infection enables microbial colonization of the airways, which results in chronic inflammation and lung damage. Our study found that bronchiectasis is a common outcome among patients with COPD and the presence of PPM in the sputum.

Patients with COPD and bronchiectasis more likely to be male (77.8% vs. 22.2%, P < 0.0003). The group of patients who had COPD with bronchiectasis was more likely to have a higher smoking index (66.9 (9.1) vs. 63.4 (8.5), P < 0.021). This correlation can be explained by the fact that the majority of subjects included in the study were male (89.3%). Patients with bronchiectasis had a longer duration of symptoms (14.1 y vs. 9.8 y, P < 0.001), a longer length of hospitalization (15.0 d vs. 10.9 d, P < 0.001), more frequent purulent sputum production (61.7% vs. 51.0%, P < 0.003) and more frequents hypercapnia respiratory failure (56.9% vs. 30.5%, P < 0.003) requiring ICU admission (35.3% vs. 10.4%, P < 0.001). These variables are associated with structural damage caused by bronchiectasis.

The most important factor associated with the presence of bronchiectasis was the isolation of PA from at least one sputum sample (HR, 2.47; 95% CI, 1.25 - 5.42; P = 0.009). PA was the most frequently isolated bacterium. The isolation of PA was significantly different between patients with COPD with bronchiectasis and patients with COPD without bronchiectasis (P < 0.002). Similar to the findings of previous studies, the isolation of PA was associated with the presence of bronchiectasis in this study [10].

In the patients with bronchiectasis, those who had tubular bronchiectasis presented with a higher level of PO_2 than patients who had other types of bronchiectasis (P = 0.003). However, there was no significant difference in PO_2 level between patients with cystic bronchiectasis and patients with mixed bronchiectasis (P = 0.845). More higher levels of inflammatory biomarkers (CRP and IL-G) were presence of cystic bronchiectasis in patients (P = 0.001). Length of hospitalization also was greatest among patients with cystic bronchiectasis (P = 0.005). ICU admission due to respiratory failure also was greatest among patients with cystic bronchiectasis (P = 0.001).

The patients with COPD and bronchiectasis have increased bronchial inflammation; longer, more severe and more frequent exacerbations; more PPM in the bronchial mucosa; and worse lung function [21]. Because the variables are associated with an increased risk of death in patients with COPD, the presence of bronchiectasis may also have a prognostic value these patients. The univariate analysis found that there was a significant difference in several of the variables between the patients who died during follow-up and those who survived. After fully adjusting for covariates, patient age, the isolation of PPM, worse lung function, hypercapnia respiratory failure, frequent ICU admission, frequent exacerbations rate and the presence of bronchiectasis were the independent risk factors of all-cause mortality in patients with COPD in this study.

The isolation of PPM from sputum samples can include PPM from a recent infection. PPM from a recent infection would be an indicator of the exacerbation of bronchiectasis, which was associated with an increase in all-cause mortality in patients with COPD in the previous study [22,23]. PPM includes bacterium and fungus, which were associated the prognosis of patients who had COPD in this study. After fully analysis of our study we found that patients who had PPM detected in their sputum were 2.57 times more likely to die than patients who did not have microorganisms in their sputum culture, independent of other variables. Our findings just increased to the suggestions about the role of PPM in the relationship between COPD and bronchiectasis.

After adjusting for covariates, patients who had bronchiectasis were 2.25 times more likely to die than those who did not have bronchiectasis in our study. This result is similar to the findings of a previous study [6]. As a prognostic factor in patients who have COPD, bronchiectasis could help physicians to establish early treatment programs to improve the prognosis of patients with COPD. The main limitation of current study was that we recruited inpatients who are admitted with COPD; these patients were more likely to have severe clinical outcomes and complications. A similar prospective study with a large sample size of stable COPD patients (outpatients) should be conducted in the future.

Conclusion

Our findings suggest that the duration of symptoms, the production of purulent sputum, the length of hospitalization, frequent exacerbations rate, poor lung function, the isolation of PA from sputum samples, hypercapnic respiratory failure and frequent ICU admission were associated with the presence of bronchiectasis in patients with COPD. The patients age, the isolation of PPM in sputum, frequent exacerbations rate, worse lung function, hypercapnia admission and the presence of bronchiectasis were independent risk factors of all-cause mortality in the survival analysis of patients with COPD.

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