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## Does bronchiectasis affect chronic obstructive pulmonary disease comorbidities?

### Abstract

**Introduction:** Chronic obstructive pulmonary disease (COPD) and bronchiectasis, chronic inflammation disorders of the bronchial tree through the mechanism of 'spill-over' of inflammatory mediators, may lead to systemic manifestations of illness of the respiratory system and comorbidities.

The aim of the study was to evaluate the frequency of coexisting COPD and bronchiectasis and influence of bronchiectasis on COPD comorbid diseases.

**Material and methods:** A post-hoc cross-sectional analysis of cohort study of 288 consecutive patients hospitalized due to acute exacerbation of COPD was performed.

**Results:** 177 males (61.5%) and 111 females (38.5%) with mean age =  $71.0 \pm 8.9$  years,  $FEV_1\%$  pred. =  $34.6 \pm 16.8$  with COPD diagnosis were studied. In this group, 29 (10.1%) patients presented with bronchiectasis confirmed by HRCT scan. COPD patients with and without bronchiectasis had similar Charlson index results (2.5 vs 2.1,  $p = 0.05$ ). COPD patients with bronchiectasis required longer hospitalization during exacerbation. COPD patients with bronchiectasis significantly more often than patients without this comorbidity revealed the features of colonization with *P. aeruginosa* (OR = 4.17,  $p = 0.02$ ).

**Conclusions:** Bronchiectasis is a relatively common comorbidity in COPD patients. COPD patients with bronchiectasis are more frequently colonized with *P. aeruginosa* comparing to non-bronchiectasis COPD patients. We did not confirm the influence of bronchiectasis on COPD comorbidities.

**Key words:** bronchiectasis, COPD, comorbidities

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### Introduction

Bronchiectasis is a relatively uncommon disease, characterized by airway dilatation and airway wall thickening associated with symptoms of persistent or recurrent bronchial infection, often secondary to various disorders causing chronic airway inflammation [1]. COPD is diagnosed based on poorly reversible airflow obstruction with an abnormal inflammatory response of the lung to cigarette smoke and other stimuli [2]. An increasing number of patients with COPD have a CT scan as part of their diagnosis and follow-up care, with a consequent impact on the detection of bronchiectasis [3]. COPD is a systemic disease with well-defined comorbidities. Diagnosis of diseases concomitant with COPD is of clinical

importance as recognition of comorbidity is a significant predictive factor [4, 5]. Generally, diseases concomitant with COPD should be treated in accordance with current detailed guidelines on particular comorbidities, and diagnosis of COPD should not result in decreased intensity of therapy [2]. However, there are clinical scenarios when the recognition of specific comorbid disease has not only prognostic value but also leads to treatment modification or a change in another medical procedure. Diagnosis of COPD in the patient with heart failure encourages doctors to order more selective beta blockers, whereas the diagnosis of concomitant osteoporosis induces them to use cautiously systemic steroids [6, 7].

It seems that recognition of comorbid bronchiectasis in COPD patients is the occasion when

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standard treatment of COPD patients' needs to be modified. When bronchiectasis is diagnosed in COPD patients, exacerbations may need longer treatment [9]. Moreover, in this group of subjects, recognition of bronchiectasis is also an adverse prognostic factor [10]. In the case of both conditions, i.e. COPD and bronchiectasis, chronic inflammation of the bronchial tree occurs, which, through the mechanism of 'spill-over' of inflammatory mediators [11], may lead to systemic manifestations of illness of the respiratory system. Anti-inflammatory treatment in COPD patients acts in many directions, one of them is the chronic use of inhaled steroids. According to the GOLD guidelines, the use of inhaled steroids should be considered in patients with a severe form of the disease and frequent exacerbations [12, 13]. In bronchiectasis, treatment with inhaled steroids is not recommended [1]. In order to reduce inflammatory status in the case of bronchiectasis in patients with frequent exacerbations, long-lasting oral [14] or inhaled [15] antibiotic therapy may be given.

In many cases it is difficult to adopt an appropriate treatment in the event of coexistence of COPD and bronchiectasis, particularly when there is a possibility of complications such as pneumonia after treatment with steroids or bacterial dysbiosis after therapy with inhaled antibiotics. It may be speculated that a pneumonia after treatment with inhaled steroids, which were observed in large post-marketing cohort studies in patients with diagnosed COPD, may be the result of the underdiagnosis of comorbid bronchiectasis [16].

There are studies on the impact of anti-inflammatory treatment on the frequency and course of concomitant diseases in COPD. There are no such studies concerning bronchiectasis.

**Aim:** The aim of the study was to evaluate the frequency of coexisting chronic obstructive pulmonary disease and bronchiectasis and influence of bronchiectasis on COPD comorbid diseases.

**Study design:** Cross-sectional, post-hoc analysis of prospective cohort study.

**Setting:** A single respiratory medicine department in the tertiary teaching hospital.

## Materials and methods

The study was based on a post-hoc analysis of data collected on a prospective basis in a single centre study, focusing on predictive factors in COPD.

The cross-sectional analysis of the group of 288 consecutive patients hospitalized due to acute exacerbation of COPD in the Second Department of

Respiratory Medicine, National Research Institute of Tuberculosis and Lung Disease was performed. The subjects were referred to the department from the Hospital Emergency Department as urgent admissions, from specialist outpatient clinics (including outpatient clinic for patients with chronic respiratory failure) or transferred from other hospitals due to difficulties in treatment.

In a hospital, all patients were assessed according to the current guidelines, COPD diagnoses were confirmed following global and local guidelines [2, 17], diagnoses of bronchiectasis were based on the high-resolution computed tomography (HRCT) scanning in line with the BTS guidelines [1]. According to the standard procedure of the original study, all patients were carefully examined for comorbidities. The diagnoses were made by a group of respiratory and internal medicine specialists and were established in compliance with current international guidelines. Comorbidity has been defined as a disease coexisting with the primary disease of interest as suggested by Sin *et al.* [18]. The list of diagnoses of each patient including comorbidities was recorded in an electronic database. After the initial treatment of acute exacerbation of COPD, all patients were offered short time hospital-based pulmonary rehabilitation. During the rehabilitation, usually about a week after hospital admission, the six-minute walk test was performed [19].

The diseases were counted and grouped into typical comorbidity groups as proposed by Charlson [20] and other authors investigating comorbidities in respiratory medicine [11, 21, 22].

Microbiological sputum cultures were ordered in all patients, according to local hospital guidelines. No procedure of induced sputum was used. As spirometry was performed during the resolution of disease exacerbation, usually a couple of days after admission to the hospital. Patients stratification according to the disease severity were performed based on the obtained results of forced expiratory volume in one second (FEV<sub>1</sub>), measured after inhalation of a 400 µg of salbutamol. The analyzed laboratory parameters included haemoglobin concentration in peripheral blood, biochemistry in serum, as well as blood gas analysis performed in arterialized venous blood, sampled directly on admission. Basing on the results of haemoglobin concentration, analysis of peripheral blood was performed and anaemia was diagnosed according to the respective World Health Organization (WHO) criteria. All physicians were free to order any additional tests and radiological assessments.

**Table 1. Clinical characteristics of subjects with COPD, with and without bronchiectasis**

	COPD without bronchiectasis	COPD with bronchiectasis	P-value
Subjects, n	259	29	—
Age (years)	70.9 ± 9.0	71.2 ± 8.6	0.88
Sex, n, M/F	160/99	17/12	0.74
GOLD combined assessment	ND	ND	—
FEV <sub>1</sub> %pred	36.1 ± 15.5	37.6 ± 16.0	0.62
Hgb (g/dL)	14.1 ± 1.7	13.9 ± 1.8	0.26
PaO <sub>2</sub> (mm Hg)	61.1 ± 11.5	57.6 ± 12.2	0.03
PaCO <sub>2</sub> (mm Hg)	45.6 ± 10.6	49.0 ± 11.8	0.10
Ht (%)	43.4 ± 5.5	43.9 ± 7.1	0.60
RBC (cells/mcL)	4.5 ± 0.6	4.6 ± 0.8	0.58
6 minute walking test (m)	264 ± 133	319 ± 102	0.03
Dyspnoea before 6 mwt (Borg scale, pts)	0.5 ± 1.0	0.5 ± 0.9	0.82
Dyspnoea after 6 mwt (Borg scale, pts)	2.4 ± 2.5	2.2 ± 2.2	0.80
Hospital treatment duration (days)	16.1 ± 11.7	21.8 ± 17.9	0.02
Charlson index	2.1 ± 1.2	2.5 ± 1.0	0.05
Creatinine (mg/dL)	0.9 ± 0.3	0.8 ± 0.2	0.46
Total cholesterol (mg/dL)	187.9 ± 43.6	189.7 ± 66.1	0.88
LDL (mg/dL)	104.8 ± 25.2	86.6 ± 25.2	0.17

The study was approved by the local Ethics Committee of National Research Institute of Tuberculosis and Lung Disease (No KB-57). Post-hoc analysis of the study was performed in 2016, using the original study database and the hospital electronic database.

### Statistical analysis

Variables are expressed as means and standard deviation in the case of quantitative variables and as percentages and absolute numbers in the case of qualitative variables. A comparison of dichotomous variables was made using the  $\chi^2$  test. The Kolmogorov-Smirnov test was used to check the normality of variables distribution. The Student t test was used to examine the difference between the means with normal distribution variables or the Mann-Whitney U test when the test of normality failed.

Odds ratio calculation was used to compute the ratio of the odds of the outcomes in both studied groups.

All results were considered to be statistically significant at  $p < 0.05$ .

Statistics analyses were performed using MedCalc software 16.2.1 (MedCalc Software, Acaciaaan 22, B-8400 Ostend, Belgium).

### Results

288 patients with the diagnosis of COPD were identified. 177 males (61.5%) and 111 females (38.5%) with mean age =  $71.0 \pm 8.9$  years, FEV<sub>1</sub>% pred. =  $34.6 \pm 16.8$  with COPD diagnosis were studied. In this group, 29 (10.1%) patients presented with bronchiectasis, all confirmed by HRCT scan performed before or during actual hospitalization (Table 1). No statistically significant differences regarding age or sex were found between the studied groups. Similarly, no differences relating to obstruction severity in COPD patients with and without bronchiectasis were discovered. Patients with COPD and bronchiectasis showed significantly lowered oxygen partial pressure, compared to the group of COPD patients without bronchiectasis ( $57.6 \pm 12.2$  mm Hg vs  $61.11 \pm 1.5$ ,  $p = 0.029$ ). Similarly, patients with COPD and bronchiectasis displayed a tendency towards increased partial pressure of carbon dioxide, compared to COPD patients without bronchiectasis, however, this time the difference was not statistically significant ( $49.0 \pm 11.8$  vs  $45.6 \pm 10.6$ ,  $p = 0.1$ ). COPD patients with bronchiectasis and without bronchiectasis had similar Charlson index results ( $2.5$  vs  $2.1$ ,  $p = 0.05$ ) (Table 2). COPD patients with bronchiectasis

**Table 2. Microbiologic characteristics of subjects with COPD, with and without bronchiectasis**

	COPD without bronchiectasis	COPD with bronchiectasis	OR	P-value	95% CI
Sputum culture with potentially pathogenic microorganism, prevalence	27.2%	46.2%	2.3	0.06	0.91–5.4
<i>Pseudomonas aerug.</i> prevalence	4.5%	16.7%	4.2	0.02	1.2–14.7
<i>Klebsiella</i> isolates, prevalence	2.6%	0%	0.7	0.80	0.03–13
<i>Acinetobacter</i> isolates prevalence	4.6%	0%	0.4	0.53	0.02–7.1

required decidedly longer hospitalization during exacerbation, compared to patients without exacerbation of the disease ( $21.8 \pm 17.9$  days vs  $16.1 \pm 11.7$ ,  $p = 0.02$ ). In a six-minute walking distance test, which was performed in the hospital ward directly after exacerbation of the disease during early rehabilitation, COPD patients with bronchiectasis covered slightly longer distance than patients without bronchiectasis —  $319 \pm 102$  vs  $264 \pm 133$  ( $p = 0.03$ ), not showing differences in dyspnea before or after the test.

COPD patients with bronchiectasis significantly more often than patients without this comorbidity revealed the features of colonization with *P. aeruginosa* (OR = 4.17,  $p = 0.02$ ). The total number of potentially pathogenic microorganisms that were cultured in the subjects was low and amounted to 29%. Individuals with bronchiectasis demonstrated larger quantities of positive results in traditional bacteriological sputum culture, i.e. 46% in the case of coexistence of COPD and bronchiectasis, and 27% for COPD without bronchiectasis (OR 2.3,  $p = 0.06$ ).

### Discussion

The authors of several previous studies concluded that the prevalence of bronchiectasis in patients with COPD is relatively high. In the study conducted by Bafadhel the prevalence of bronchiectasis was shown to be 27% [23]. In this study, all patients were actively screened for bronchiectasis with HRCT. Contrary to that, in the ECLIPSE cohort study, only 4% of patients with COPD had bronchiectasis [24]. Such difference can be explained by the inclusion criteria of the ECLIPSE cohort, which excluded other pulmonary comorbidities at baseline. In our study we have found that 29 patients from the group of 288 COPD patients had been diagnosed with comorbid bronchiectasis. In a recent

metaanalysis of the coexistence of COPD and bronchiectasis, Du [25] and Ni [26] summarized the data. In this metaanalysis the prevalence of bronchiectasis in different articles varies between 19% and 50%. According to the authors such a relatively high prevalence depends on the respective prevalence of COPD and bronchiectasis in the population under consideration. During the discussion of coexistence of COPD and bronchiectasis some authors concluded that bronchiectasis in patients with primary COPD can be considered a phenotype of the COPD spectrum. As suggested by Hurst, further work is needed to define pathogenesis and clinical consequences of this phenotype [3].

The discussion about the frequency of bronchiectasis in patients with a diagnosis of chronic obstructive pulmonary disease is of clinical importance due to the difference in treatment management and prognosis. Due to the methodology of conducted clinical trials in COPD patients, only some subjects who meet the criteria of COPD diagnosis may be included in the randomized trials. The criteria that exclude from such kind of trials are usually comorbid pulmonary diseases such as bronchiectasis. Correspondingly, in the case of clinical trials testing drugs in patients with bronchiectasis, only a small part of the patient population may be included in the trial in which evaluation of therapeutic effectiveness of the medication is planned. According to Chalmers *et al.*, patients enrolled in randomized controlled trials concerning bronchiectasis are only partially representative of patients in clinical practice, for example only 15% of patients were eligible for trials with inhaled antibiotics [27]. These limitations of clinical trials lead to problems in choosing the right inhalation therapy for patients with COPD and bronchiectasis especially the safety of the use of inhaled steroids in COPD and bronchiectasis. In the absence of controlled clinical trials, observa-

**Table 3. Most frequent comorbidities in patients with COPD with and without bronchiectasis**

Disorder, prevalence	COPD without bronchiectasis	COPD with bronchiectasis	OR	P-value	95% CI
Hypertension	66.0%	52.6%	0.81	0.58	0.35–1.81
Obesity	13.1%	3.6%	0.27	0.21	0.03–2.01
Thyroid diseases	15.1%	16.0%	1.04	0.92	0.31–3.22
Diabetes	20.5%	20.8%	1.01	0.97	0.31–2.88
Cancer/neoplasm	2.0 %	0%	0.78	0.87	0.06–22.62
Anaemia	34.2%	45.1%	1.57	0.24	0.72–3.43
Coronary heart disease	11.6%	11.5%	0.99	0.9	0.28–3.49
Gastric/duodenal ulcer	10.2%	3.6%	0.35	0.31	0.32–3.43
Chronic kidney disease	5.7%	0%	0.29	0.39	0.22–4.93
Home oxygen therapy	7.5%	16.3%	2.11	0.19	0.61–6.86
Chronic heart failure	8.8%	3.6%	0.40	0.38	0.12–3.14

tional studies are of great importance. In several large cohort studies based on administrative data of a big number of patients, it was found that the treatment with inhaled steroids in people with COPD may result in an increased frequency of pneumonia [16, 28]. Although such risk has been already presented in detailed analyses of randomized clinical trials, the problem arose in real-life data analysis [28]. It is possible that the difference in the prevalence of pneumonia in COPD subjects that was observed in randomized and big cohort trials is caused by a considerable proportion of patients with bronchiectasis who were excluded from randomized trials and who constitute a noticeable percentage of COPD patients observed in usual clinical practice. There also exists the possibility that as CT is not a routine examination in all COPD subjects, and the clinical image of both diseases may be similar, treatment with inhaled steroids is often offered to patients who, due to bronchial lesions such as bronchiectasis, definitely should not receive such treatment.

In the analysis present, both groups of patients stayed in the hospital for a relatively long time — 16.7 days, which was partly associated with the protocol of the primary trial including inpatient respiratory rehabilitation, which was introduced directly after COPD exacerbation. The rehabilitation lasted about a week depending on the clinical condition of the patient. However, patients with coexisting COPD and bronchiectasis stayed in hospital for a notably longer time. Such outcomes were probably affected by respiratory insufficiency — patients in whom bronchiectasis was diagnosed had the features of more severe hypoxemia.

Another element influencing their clinical condition and the need for longer hospitalization were concomitant diseases. In our study, the difference in the Charlson index results between the group of COPD with and without bronchiectasis did not reach statistical significance ( $p = 0.05$ ). In addition, the frequency of most common comorbidities was similar in both groups (Table 3). The frequency of observed concomitant diseases with COPD in our group generally corresponds to comorbidities observed in other studies [29].

In the present study, we found that the group of subjects with coexisting COPD and bronchiectasis had a slightly lower oxygen partial pressure, compared to COPD patients in whom bronchiectasis was not recognized. It may imply that the bronchial lesions which occur in patients with bronchiectasis are an additional factor influencing the severity of the disease. However, patients with COPD and bronchiectasis have shown better exercise tolerance compared to patients with COPD but without comorbid bronchiectasis. Unfortunately data collected in the present study does not allow to precisely elucidate the mechanisms of exercise tolerance in both studied groups.

Sputum was examined in all subjects included in the study. The proportion of positive culture in the group of COPD patients amounted to 30%, whereas in the group of subjects with COPD and bronchiectasis it reached up to 46% but due to the limited number of patients in the group with bronchiectasis, this difference was not statistically significant. Of note is a substantial

proportion of isolated *P. aeruginosa* in the case of patients with comorbid bronchiectasis, which is also similar to the values observed in other researches [10].

But looking from the actual perspective at the studies that we had conducted a few years back, we have to emphasize that the attempts to correlate sputum cultures with comorbidities are ineffective. In order to analyze the correlation between the bacterial load of the bronchial tree, the parameters of inflammatory status and comorbidities, newer genetic tests, as bacterial genome sequencing [30] should be used.

### Potentially confounding factors of the study

The original idea of the study was to estimate prognostic factors in acute exacerbation of COPD and this study design means that its results cannot be applied to the entire population; it was not an epidemiological study. On the other hand, the present study can be valuable in identifying a real problem, i.e. underdiagnosis of bronchiectasis in the population of COPD patients.

### Conclusion

Bronchiectasis is a relatively common comorbidity in COPD patients. COPD patients with bronchiectasis are more frequently colonized with *P. aeruginosa* comparing to non-bronchiectasis COPD patients. We did not confirm the influence of bronchiectasis on COPD comorbidities.

### Conflict of interest

None declared

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