**Relationship between clinical and radiological signs of bronchiectasis in COPD patients: Results from COSYCONET**

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**Abstract**

Background: Bronchiectasis might be frequently present in COPD but masked by COPD symptoms. We studied the relationship of clinical signs of bronchiectasis to the presence and extent of its radiological signs in patients of different COPD severity.

Methods: Visit 4 data (GOLD grades 1-4) of the COSYCONET cohort was used. The chest CT scans were evaluated semi-quantitatively for bronchiectasis in 6 lobes using a 3-point scale (0: absence, 1: ≤50%, 2: >50% bronchiectasis involvement for each lobe), yielding a total score of 0-12. We also included data from disease-specific questionnaires, medication, and lung function.

Results: 1176 patients were included (61% male, mean age 67.3 y), among them 38 (3.2%) with patient-reported physicians’ diagnosis of bronchiectasis and 76 (6.5%) with alpha1-antitrypsin deficiency (AA1D). CT scans were obtained in a sub-group of 429 patients. Within this sub-group, any signs of bronchiectasis were found in 46.6% of patients, whereby ≤50% bronchiectasis occurred in 18.6% in ≤2 lobes, in 10.0% in 3-4 lobes, in 15.9% in 5-6 lobes; >50% bronchiectasis in at least 1 lobe was observed in 2.1%. There was no dependence on GOLD grades. Scores ≥4 correlated with an elevated ratio FRC/RV, while there were no associations with inflammatory indices (CRP, leukocyte count). The clinical diagnosis of bronchiectasis correlated with phlegm and cough and with radiological scores of at least 3, optimally ≥5. AA1D was also associated with radiological signs of bronchiectasis but only borderline with the clinical diagnosis.

Conclusion: In COPD patients, clinical diagnosis and radiological signs of bronchiectasis (regardless of extent) showed only weak correlations. Correlations became significant with increasing severity of bronchiectasis, i.e. CT scores above a threshold value, implying radiological alterations in several lobes. This indicates the importance of reporting both presence and extent of bronchiectasis on CT. Patients with radiological scores≥4 showed a slightly reduced RV/FRC ratio as the only functional alteration specific for bronchiectasis, indicating less air trapping relative to hyperinflation. Further research is warranted to refine the criteria for CT scoring of bronchiectasis and to determine the relevance of radiologically but not clinically detectible bronchiectasis and their possible implications for therapy in COPD patients.

**Introduction**

Bronchiectasis has been described as an important comorbidity in patients with COPD [1]. Both disorders show a clinical and diagnostic overlap in terms of sputum production and increased susceptibility to repeated exacerbations or persistent infections. Therefore, these patients present a clinical challenge especially at initial diagnosis. According to the GOLD classification [2], in addition to appropriate clinical signs and history, alterations of lung function play a fundamental role in the diagnosis of COPD, based on the assumption of a more or less fixed airway obstruction. In contrast, clinical signs can raise the suspicion of bronchiectasis but the key to diagnosis is the detection of airway dilatation and bronchial wall thickening with computed tomography (CT). Clinical significance of bronchiectasis is assumed, if bronchiectases detected on CT and symptoms of persistent or repeated infections are present [Lancet submitted]. While imaging with chest CT is becoming more and more becoming part of the primary diagnostic evaluation of COPD, the diagnosis of bronchiectasis is becoming more and more common among these patients.

Although bronchiectasis as a comorbidity has been frequently described in COPD patients, its prevalence estimates are widely varying, and values between 4% and 72% have been reported [3]. There are various reasons for this. For example, studies have used different methodologies and patients with bronchiectasis have been excluded in a number of COPD studies [4]. A recent publication reported bronchiectasis in 19.9% of lung-healthy individuals, compared to 35.1% of patients with severe COPD of the same age [5]. In COPD, the presence of clinically relevant bronchiectasis appears to be associated with alterations in clinical characteristics, such as lower BMI and higher age, beyond the increased burden from sputum production and exacerbations [3]. In addition to functional and clinical limitations, these patients also show increased colonisation with P. aeruginosa and greater signs of local and systemic inflammation [6-8]. As a result, COPD patients with bronchiectasis experience an increased risk of mortality. The presence of bronchiectasis also modifies therapy decisions in COPD, e.g. in the sense that inhaled corticosteroids should be prescribed with caution [9].

Paradoxically, the challenge of diagnosing bronchiectasis in COPD might become more important, as the radiological detection becomes more sensitive, raising the possibility of over-diagnosis in case of clinically irrelevant bronchiectasis. Based on these considerations, we analysed the relationship between clinical, functional and radiological signs of bronchiectasis, with the specific aim to determine the degree of radiological alterations corresponding to clinically detectable signs of bronchiectasis. The analysis was based on data of the large COPD cohort COSYCONET (**CO**PD and **Sy**stemic Consequences-**Co**morbidities **Net**work) focusing on the role of comorbidities [10]. In this multi-center study, prospective radiological evaluations were available in a sub-cohort.

**Methods**

Data from patients of GOLD grades 1–4 [2] obtained in visit 4 of the COSYCONET cohort were used, corresponding to a subset of n = 1176 patients of the n = 2741 patients recruited in visit 1 [10]. In addition to visit 4 data, selected information from visit 1 was used in the analysis. The COSYCONET study was approved by the ethical committees of all study centers, and all patients gave their written informed consent [10].

**Assessments**

Study protocol and assessments of COSYCONET have been described previously [10]. Similar to other comorbidities, the comorbidity “bronchiectasis” was assumed on the basis of patients’ reports of a physician-based diagnosis. C-reactive protein (CRP) and leucocyte count assessed by standard procedures were available as laboratory markers [11]. Spirometric and body plethysmographic lung function data comprised forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), residual volume (RV), functional residual capacity (FRC), total lung capacity (TLC), all in percent predicted, as well as the ratios FEV1/FVC, RV/TLC, FRC/TLC and FRC/RV. Furthermore, values of single-breath diffusing capacity for carbon monoxide (TLCO and KCO) were included. Predicted values of spirometric measures were taken from the Global Lung Initiative (GLI) [12], those of body plethysmography from ECSC [13], those of TLCO and KCO from GLI [14].

The determination of symptom burden was based on the COPD assessment test (CAT) and the St. George’s Respiratory Questionnaire (SGRQ). The modified Medical Research Council dypnea scale (mMRC) was used to define GOLD groups A-D [15], in combination with the exacerbation risk based on the 12-month history of exacerbations of all severities, including hospitalization [2, 16]. The intake of potentially relevant medication, i.e. inhaled and systemic corticosteroids, antibiotic treatment and anti-cholinergic treatment, was assessed by structured interviews [11].

At the time of visit 4, 602 patients in 16 study centers were enrolled in the sub-study SP7 of COSYCONET and received additional computed tomography (CT) scans of the thorax in inspiration and expiration [10] . The images were evaluated by experienced thoracic radiologists. Regarding bronchiectasis, a semi-quantitative visual evaluation at the pulmonary lobe level was performed using a 3-point scale for each lobe (0: no bronchiectasis, 1: ≤50% bronchiectasis, 2: >50% bronchiectasis). Three lobes on each side were evaluated, counting the lingula as "left middle lobe" analogous to the middle lobe, which resulted in a total radiological bronchiectasis score of 0-12.

**Statistical analysis**

Data are presented as numbers and percentages, or mean values and standard deviations (SD). Comparisons between groups (patients with vs. without CT) were performed by the Mann-Whitney-U test, or by chi-square-tests in case of categorical variables. The associations between variables were evaluated by linear and logistic regression analyses comprising one dependent and multiple independent variables. In the respective analyses, age, gender and BMI were always included as confounders. P values less than 0.05 were considered as significant. All analyses were performed with the software SPSS Version 26 (IBM Corp., Armonk, NY, USA).

**Results**

**Study population**

Patients’ characteristics are given in table 1A. Of the 1176 COPD patients participating in visit 4 (mean age 67.3 y, 61.1% males), 103/521/420/132 patients showed GOLD grades 1-4, while GOLD grades A/B/C/D were shown by 407/249/193/321 patients. Overall, 429 patients had CT scans that could be evaluated for the presence and degree of bronchiectasis. Patients with CT scans were slightly younger and showed slightly lower values in ITGV, RV, RV/TLC and CAT score, as well as slightly higher values for TLCO (p<0.05) compared to those without CT scans. Table 1B shows the respective patients’ characteristics according to the radiological presence of bronchiectasis.

Table 2 shows the distribution of bronchiectasis scores (0-2) over the 6 lobes analysed, table 3 the distribution of sum scores 0-12 versus the patient-reported diagnosis of bronchiectasis. Among the 1176 patients, 38 patients (3.2%) had a patient-reported physicians’ diagnosis of bronchiectasis and 76 (6.5%) of alpha1-deficiency (AA1D), while the numbers for patients with CT scan were 10 (2.3%) and 36 (8.4%), respectively.

**Assessment of symptoms and exacerbations**

Among all CAT items, only the questions for cough (p=0.026) and sputum production (p<0.001) were significantly associated with the physician-based diagnosis of bronchiectasis, while the question for “I am confident leaving my home despite my lung condition” was borderline significant (p=0.050). Also, the SGRQ questions regarding phlegm, cough and phlegm, and physical activity were significantly associated with the physician-based diagnosis of bronchiectasis (p<0.05 each).

There was no association between the diagnosis of bronchiectasis and elevated exacerbation risk, expressed via GOLD groups C and D (p=0.456), while there was a tendency towards significance (p=0.066) regarding the association with elevated symptom burden expressed via GOLD groups B and D.

The physician-based diagnosis of bronchiectasis was not significantly linked to the inflammatory markers CRP and leucocyte number in peripheral blood.

**CT-based diagnosis of bronchiectasis**

In 429 patients at visit 4, CT scans were available, which showed signs of bronchiectasis in 46.6% of patients, with less than 50% bronchiectasis in 2 lobes in 27.5%, in 26.1% in 4 lobes, in 13.0% in 6 lobes, and more than 50% bronchiectasis in at least 1 lobe in 2.1% of patients (tables 2 and 3). The prevalence of bronchiectasis was higher in the middle and right lower lobe, as well as lingula and left lower lobe (table 2). For the purpose of illustration, figure 1A shows a CT scan of a patient with a total bronchiectasis score =4, and figure 1B shows typical lobe picture with a score of 2.

*Patients’ characteristics and comorbidities*

Patients without vs. with radiological score ≥1 showed no significant differences in sex, smoking status (active vs. ex- or never-smoker), pack years, or the presence of comorbidities including asthma, lung fibrosis, heart failure, hypertension, gastrointestinal disorders, ischemic heart disease and sleep apnoea (p>0.05 each). Patients with radiological score ≥1 tended to be older (mean age 67.1 vs. 65.4 y without bronchiectasis, p=0.0 54) and showed a significantly reduced BMI (mean 25.8 vs. 27.4 kg/m² without bronchiectasis, p=0.022). The presence of AA1D was associated with radiological score ≥1 (p=0.014), with stronger associations emerging for score cut-off values ≥3 up to ≥5 (p<0.005 each). In contrast, the clinical diagnosis of bronchiectasis showed no significant relationship to AA1D.

*Lung function*

The comparison of patients with vs. without signs of bronchiectasis (sum score ≥1 versus 0) showed no significant differences in FEV1%predicted, FVC%predicted, FEV1/FVC, RV/TLC, FRC%predicted, RV%predicted, TLCO%predicted and KCO%predicted. Repeating the analyses with increasing cut-off values for the bronchiectasis sum score revealed that patients with a score≥4 showed relatively high FRC/RV compared to those without, when adjusting for age, sex, BMI and lung size in terms of TLC%predicted as covariates (p=0.016). This was in parallel with a significant relationship between a bronchiectasis score≥4 and the ratio RV/TLC (p=0.048) but not FRC/TLC (p=0.978), again taking into account adjustment. Figure 2 shows the comparison of the RV/FRC ratio between patients with vs. without scores ≥4, adjusted for age, sex, BMI and TLC%predicted. We found no associations between GOLD grades 1-4 and the radiological presence of bronchiectasis independent of bronchiectasis severity (sum score ≥1 or sum score ≥4). For high cut-off values ≥5, the numbers of patients exceeding the cut-off became too small to identify significant differences, while for smaller cut-off values (<4) the effects were still present but weaker.

*Clinical diagnosis and signs, biomarkers*

The clinical diagnosis of bronchiectasis was associated with radiological findings for scores at cut-off values ≥3 (p=0.002), with best findings for scores of ≥5 (p<0.001).

In unadjusted analyses, there were no significant associations of CT-based diagnosis of bronchiectasis (score cut-off ≥1) and the symptoms of sputum production and cough according to the CAT items, as well as the respective SGRQ questions (chi-square test). Similar results were obtained when using a cut-off value ≥4 for the radiological findings. Unadjusted analyses as well showed no associations between radiological bronchiectasis (score cut-off ≥1) and elevated exacerbation risk (GOLD groups C/D vs. A/B) or elevated symptom burden (GOLD groups B/D vs. A/C) (p=0.840 and p=0.707, respectively, chi-square test). When using a bronchiectasis-score cut-off ≥4, there were also no significant associations. In contrast to the radiological diagnosis, the clinical diagnosis of bronchiectasis correlated with phlegm and cough according to the CAT score (p<0.001 and p=0.026, respectively).

There was no link between the radiological score (cut-off ≥1) and the biomarkers (CRP and leukocyte count, Mann-Whitney-U-test). This was also true when using higher cut-off values than 1.

**Association with pharmacological treatment**

Treatment of the respiratory disease by LABA, LAMA, ICS and their combinations, including triple therapy, showed no significant, internally consistent, associations between the physician-based diagnosis of bronchiectasis or the radiological diagnosis (score cut-off ≥1). Moreover, the intake of oral corticosteroids and antibiotics was not significantly related to a radiological score ≥1, and this was also true for other cut-off values. In contrast, the clinical diagnosis of bronchiectasis showed associations, as patients with bronchiectasis had more often antibiotics (p<0.001) and less often oral corticosteroids (p=0.013).

**Discussion**

In the present analysis, we investigated the relationship between clinical and functional signs of bronchiectasis and a systematic radiological evaluation in a large COPD cohort. Not all patients were examined with CT but the proportion of patients with the clinical diagnosis of bronchiectasis did not significantly differ between patients with and without CT scan, thus the CT group was considered a representative sample. The clinical, physician-based diagnosis, as reported by the patients, turned out to be of questionable value, whereas the CT-based diagnosis appeared more informative. On the other hand, a minimum radiological score was needed to find associations with symptoms and functional alterations typical for bronchiectasis. The radiological score showed only weak relationships to the clinical diagnosis of bronchiectasis, probably due to the small number of patients, however a significant relationship to the diagnosis of AA1D. The discrepancy between clinical and radiological diagnosis of bronchiectasis has two implications. First, there may be clinical under-diagnosis of bronchiectasis in COPD, if radiological findings are taken as criterion. On the other hand, a purely radiological diagnosis might be oversensitive. If this should be correct, it would suggest that in the process of diagnosing bronchiectasis in COPD, clinical signs such as sputum production and cough should be combined with radiological alterations only if these exceed a minimum value, which in our study was about one third of the maximum range of the score.

In a recent consensus paper, the diagnostic criteria of clinically relevant bronchiectasis have been described (lit lancet sub). The diagnosis should always include at least two of the following symptoms (1) cough at most days of the week, (2) sputum production at most days of the week, (3) history of exacerbations (lit lancet sub). It has often been argued that CT scans provide an opportunity for early detection of bronchiectasis independent of symptoms [1] but our results sound a note of caution about this. There is an overlap of symptoms and clinical signs between COPD and bronchiectasis, and the CT-derived presence of bronchiectasis could also be also a feature of COPD [17]. Therefore, the differential diagnosis poses a continuing clinical challenge.

The characteristics of our study cohort were similar to those described in previous investigations [3]. For example, our patients with bronchiectasis (radiological score ≥ 1) tended to be older, and to be males compared to those without bronchiectasis. Bronchiectasis in COPD is usually located in both pulmonary bases (52-81%) and bilateral (52-67%), and shows moderate degrees in radiological analyses of severity [6, 7, 18-20]. The pattern observed in the present study was similar to these findings, including the distribution of scores over lobes and the maximum scores observed (see table 3). In contrast to the literature [8, 21-23], we did not observe a relationship to exacerbation risk, at least according to the categorization GOLD CD vs. A/B. This might have been due to the relatively high treatment intensity [24] and adherence to treatment [25] in COSYCONET. An additional factor might have been that in the majority of patients bronchiectasis was not prominent according to the radiological findings; therefore, the exacerbation history was probably dominated by the COPD and not by bronchiectasis. In the patients without radiological signs and without physician-based diagnosis of bronchiectasis, the distribution over GOLD groups ABCD was 40.7/19.9/16.8/22.6%, whereas in patients with either radiological signs or appropriate history the distribution was 34.6/19.0/19.9/26.0%. Thus, both groups showed only minor differences. For patients with bronchiectasis in the absence of COPD, an exacerbation frequency of 1.8-3 per year has been reported [26], whereby only part of them (26.6-31.4%) led to hospitalization over 2-year follow-up [26]. This frequency is similar to that indicated by the distribution over GOLD grades A-D in out cohort, underlining that it is difficult to infer the presence of bronchiectasis from exacerbations in patients with COPD. An additional, well-known problem when comparing data is the heterogeneity in the definitions of exacerbations.

Airway wall alterations in patients with COPD are usually described as mild and diffuse, whereas bronchiectasis may also show localized alterations, with mild to severe varicose or cystic changes [1]. In line with this, our data indicated that only a very small proportion of COPD patients showed severe alterations in the sense of involvement of more than 50% per pulmonary lobe (see table 3). We also evaluated a summary bronchiolitis score comprising mosaic pattern, air trapping and mucus plugging, which was significantly (p=0.028, Spearman correlation) related to the bronchiectasis sum score but not to the presence of dyspnoea, sputum production, symptom burden or exacerbation history.

The mild CT morphological changes were in accordance with the functional status. We did not observe any significant differences in the severity of airway obstruction, lung hyperinflation, or CO diffusing capacity. There was, however, a functional sign of bronchiectasis in terms of a slightly reduced RV/FRC ratio, which was indicative of less air trapping relative to hyperinflation in patients with radiological scores≥4. This might have been associated with a more airway-based phenotype in COPD patients and less peripheral destruction associated with air trapping.

Regarding inhaled medication, our data did not find significant differences between COPD patients with vs. without bronchiectasis (based on either radiological score ≥1 or clinical diagnosis). Since only a radiological score ≥4 was associated with symptoms and thus a clinically apparent bronchiectasis, the leading clinical picture in the majority of patients was the presence of COPD and the prescribed medication can be considered as adequate.

The following conclusions for clinical practice may be drawn from our results. In case of clinical evidence for the presence of bronchiectasis, especially from symptoms, CT imaging with semi-quantitative scoring should be performed to substantiate the clinical suspicion in the presence of COPD. Presence of bronchiectasis as an incidental finding in patients with no clinical diagnosis of bronchiectasis, in particular with radiological score ≥4 (corresponding to 4 lobes ≤50%, or 2 lobes >50%, or 1 lobe >50% and 2 lobes ≤50% involvement) should trigger attention to specific symptoms and according treatment, if applicable (e.g. adjustment of inhalation therapy, removal of ICS, or extension of antibiotic therapy in the context of exacerbations) [1]. The potential clinical relevance of the radiologically detectible, but clinically not evident bronchiectasis with radiological scores ≤4 remains unknown and warrants further clinical research. According to our results, these do not appear to be associated with a higher symptom burden or exacerbations, thus the treatment for these patients should follow primarily COPD guidelines.

**Limitations**

Despite the large sample sizes in the total cohort and the sub-cohort with CT scans, the statistical power for analyses of risk factors and additional characteristics of bronchiectasis was limited. For example, only 22 patients reported the diagnosis of tuberculosis, a known risk factor for bronchiectasis; due to the small sample size we did not further analyse this group of patients. The radiological bronchiectasis score used is not validated, but the CT scans were evaluated by very experienced radiologists. In principle, sputum diagnostics would have been desirable but spontaneous sputum was available in only n=104 patients, whereby the presence of 52 microorganisms was analysed in the laboratories of the study centres. Due to the small sample size and the heterogeneity of results, we could not establish associations between the microbiological pattern and either the clinical diagnosis of bronchiectasis or the radiological score. Furthermore, the study was cross-sectional with non-interventional design, so that no causality can be inferred. The strength of our study was the high quality of clinical and functional data and the prospective evaluation of CT examinations that were also subject to strict standardization and quality control, ensuring the comparability between study centers.

**Conclusion**

Our findings obtained in a large COPD cohort showed a high prevalence of CT findings consistent with bronchiectasis. However, symptoms, clinical diagnosis and radiological detection of bronchiectasis (regardless of extent) were only weakly correlated. Associations with symptoms and clinical diagnosis became stronger after quantitation of CT findings based on the visual semi-quantitive score. It appeared that only for patients with sum scores of at least one third of the maximum score for bronchiectasis on CT, clinical significance could be assumed. These findings underline the importance of a quantitative approach when reporting bronchiectasis on CT in COPD patients, as prerequisite for a COPD-specific combined clinical and radiological evaluation of bronchiectasis. The differentiation between bronchiectasis as component of COPD itself, or as separate entity and comorbidity of COPD, remains a diagnostic challenge, since clinical characteristics are overlapping. Further research is warranted to study the clinical relevance of the radiologically detectible, but clinically hidden bronchiectasis and their possible implications for medication in COPD patients.

**Literature**

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