The Association Between Bronchiectasis and Chronic Obstructive Pulmonary Disease: Data from the European Bronchiectasis Registry (EMBARC)

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Short title: COPD and Bronchiectasis association in the EMBARC registry

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Scientific Knowledge on the Subject

Bronchiectasis and COPD are associated conditions and reports suggest when both are present, patients have worse clinical outcomes. There is confusion over these diagnostic labels, however, as Bronchiectasis may lead to airflow obstruction independently of external exposures as a result of a cycle of inflammation, infection and impaired mucociliary clearance. In an effort to standardise the diagnosis of COPD the EMBARC consortium published the ROSE criteriaof bronchiectasis (BE) and COPD association. The ROSE criteria (radiological bronchiectasis(R), obstruction: FEV1/FVC ratio <0.7 (O), symptoms (S) and exposure: ≥10 pack year smoking history (E) allows objective validation of clinical diagnosis of BE-COPD association.

What this study adds to the field: This study shows that COPD is commonly reported in patients with bronchiectasis, with 25.5% of bronchiectasis patients carrying a clinician assigned co-diagnosis of COPD in a registry of nearly 17000 patients from 28 countries. Patients with a clinician assigned co-diagnosis of COPD had more exacerbations, worse symptoms and more severe disease. Using the objective diagnostic criteria, however, nearly ¼ of patients with a COPD label did not have airflow obstruction and nearly 1/3 did not have a history of >10 pack years smoking. Collectively, an objective diagnosis of COPD was made in 55% of patients carrying a clinical diagnostic label of COPD. Patients with a label of COPD had worse long term outcomes regardless of whether they met the objective criteria, suggesting that the label of COPD identifies patients with bronchiectasis at high risk of poor outcomes which was not strongly related to the presence of airflow obstruction or smoking history. Our data suggests the label of COPD is frequently used inappropriately in patients with bronchiectasis.

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Abstract

Rationale and Objective: Using the EMBARC registry, the largest prospective bronchiectasis dataset in the world, we investigated the prevalence of COPD associated with bronchiectasis and its relationship with clinical outcomes. We further investigated the impact of implementing the standardised ROSE criteria (radiological bronchiectasis(R), obstruction: FEV1/FVC ratio<0.7 (O), symptoms (S) and exposure:≥10 pack year smoking (E), an objective definition of BE-COPD association.

Methods: Analysis of the EMBARC registry, a prospective observational study of patients with CT confirmed bronchiectasis from 28 countries. The ROSE criteria were used to objectively defined BE-COPD association. Key outcomes during up to 5-years follow-up were exacerbations, hospitalization and mortality.

Measurement and main results: 16730 patients with bronchiectasis were included. 4336 had a clinician assigned co-diagnosis of COPD and these patients had more exacerbations, worse quality of life and higher severity scores. We observed marked overdiagnosis of COPD. 22.2% of patients with a diagnosis of COPD did not have airflow obstruction and 31.9% did not have a history of ≥10 pack years smoking. Therefore the proportion meeting the ROSE criteria for COPD was 2157 (55.4%). Compared to patients without COPD, patients meeting ROSE criteria had increased risk of exacerbations and exacerbations resulting in hospitalisation during follow-up (IRR 1.25 95%CI 1.15-1.35 and 1.69 95%CI 1.51-1.90 respectively).

Conclusions: The label of COPD is often applied to bronchiectasis patients without objective evidence of airflow obstruction and smoking history. Patients with a clinical label of COPD have worse clinical outcomes.

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Introduction

Bronchiectasis is both a radiological term denoting permanent dilatation of the bronchi, and a clinical syndrome of cough, sputum production and recurrent respiratory infections.[1] The clinical features of bronchiectasis significantly overlap with those of chronic obstructive pulmonary disease(COPD).[2,3] The association between these two conditions is well recognised.[2–4] The prevalence of radiological bronchiectasis in patients with COPD is reported to be highly variable, ranging from 4% to 72% in different studies.[2–4] Where patients have labels of both COPD and bronchiectasis, clinical outcomes and phenotype are reported to be worse, with more frequent exacerbations and higher mortality.[4] The inconsistency in different studies, however, reflects a lack of standardisation in the diagnosis of both bronchiectasis and COPD as well as the low sample size of many studies. The “chicken and egg” relationship of COPD and bronchiectasis has the potential to create confusion. Bronchiectasis is frequently reported in patients with a primary diagnosis of COPD, and bronchiectasis can cause fixed airflow obstruction through progressive lung damage.[5–7]

COPD is defined by the Global Obstructive Pulmonary Disease committee as a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum production and/or exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction[8] While it is recognised that COPD has multiple causes, in Europe, exposures causing COPD are most commonly tobacco smoke. COPD is defined physiologically by the presence of airflow obstruction that is persistent after treatment with bronchodilators.[9] Most COPD clinical trials require the presence of fixed airflow obstruction and a minimum smoking history to define COPD.[10]

An international consensus aimed at standardizing the definition of bronchiectasis and COPD association proposed the ROSE criteria consisting of radiological bronchiectasis(R), obstruction defined by an FEV1/FVC ratio <0.7 (O), symptoms (S) and exposure to a minimum of 10 pack year smoking history (E). Patients having all 4 criteria may be considered to have potentially overlapping

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disorders.[3] There have been no studies using these standardized criteria to define the bronchiectasis/COPD association.

Using the EMBARC registry[11], the largest prospective bronchiectasis dataset in the world, we investigated the prevalence of COPD associated with bronchiectasis and its relationship with clinical outcomes. We further investigated the hypothesis that COPD would be over-diagnosed in bronchiectasis patients and that implementing the standardised ROSE criteria[3] would more accurately identify the true prevalence and impact of Bronchiectasis/COPD association.

Methods

The European Bronchiectasis Registry (EMBARC) is a prospective observational study of patients with computed tomography confirmed bronchiectasis. The present analysis includes data from 28 countries in Europe and Israel.[12] The study is approved by the ethical committee in the host country (UK) and by institutional review boards or ethics committees in all countries and regions in which the study is conducted. A detailed protocol of the study has been previously published.[11]

Data collection

Patient enrolment commenced in January 2015 and recruitment is open ended and ongoing. Patients enrolled up to April 2022 were included for the purposes of this analysis. Patient data were collected annually using a standardised case report form. Data on clinically indicated sputum samples sent during clinical stability and exacerbation were collected and patients classified according to whether they had isolated specific bacteria in any sample in the previous 12 months.[12] Radiological severity was evaluated in the patients most recent CT scan using the modified Reiff score which scores each affected lobe, with the lingula treated as a separate lobe, and classifies the most severe bronchiectasis per lobe into cylindrical (1 point), varicose (2 points) or cystic (3 points) for a maximum of 18 points.[13] Disease severity was evaluated using the bronchiectasis severity index

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(BSI).[14] Exacerbations were defined as use of antibiotics for acute respiratory symptoms and were recorded from a combination of patient history, hospital and prescription records.[15] Symptoms were evaluated using the Quality of life bronchiectasis questionnaire version 3.1 using validated translations.[16]

Lung Function testing

Spirometry was performed at baseline and at each follow-up visit according to ATS/ERS standards. For the primary analysis predicted values and % of predicted were calculated using ECCS reference equations.[12] The EMBARC registry is an observational study of routine clinical care and therefore post-bronchodilator spirometry was not mandatory. For the purposes of analysis post-bronchodilator spirometry data have been included where available, but pre bronchodilator data have been included in the primary analysis. A sensitivity analysis incorporating only post-bronchodilator spirometry data is presented.

COPD diagnosis

COPD diagnosis was recorded in two fields within the EMBARC dataset. COPD could be reported as an aetiology of bronchiectasis (in the opinion of the investigator), or as a co-morbidity. For the purposes of this analysis the primary comparison was between patients with any diagnosis of COPD (aetiology or co-morbidity). The diagnosis of COPD could be either from medical records or the investigators judgement.

The ROSE criteria were applied in the dataset to objectively define COPD-bronchiectasis association. As patients require both radiological bronchiectasis and compatible symptoms to be enrolled in the study, the radiology and symptom criteria of ROSE are already met and therefore the objective criteria as applied to the EMBARC dataset require a smoking history of at least 10 pack years and the presence of an FEV1/FVC ratio less than 0.7.[3]

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The analysis of the impact of COPD on patient characteristics and outcomes was performed in two ways, firstly using clinically defined COPD vs no clinically reported COPD. Secondly the ROSE criteria were applied to divide patients into 4 groups. Patients in whom the clinician had diagnosed COPD and with airflow obstruction and a history of 10 or more pack years (COPD+ ROSE+), diagnosed COPD without airflow obstruction or a smoking history (COPD+ ROSE-), no diagnosed COPD but with airflow obstruction and 10 or more pack years smoking history (COPD- ROSE+) and patients without a diagnosis of COPD or objective evidence of COPD (COPD- ROSE-).

Long term clinical outcomes

Data are collected for up to 5 years on an annual basis for calculation of clinical outcomes. Since patient enrolment began in 2015, patients have up to 5 years of follow-up at the time of writing, although the dataset includes patients enrolled through to 2022 who have not yet had a follow-up visit. Statistical analysis of relevant endpoints takes account the duration of follow-up. Relevant clinical outcomes were survival, exacerbation frequency and hospitalization due to severe exacerbations.

Statistical analysis

Summary data are presented as median with interquartile range. Comparisons of two groups used the Mann Whitney U test with comparisons of more than two groups performed using the Kruskal-Walis test. Proportions were compared using the Chi Square test or the Fishers exact test if any cell contained a value less than 10. Exacerbation frequency and frequency of severe exacerbations requiring hospital admission over time were studied using a negative binomial model with time in study as an offset. Survival analysis was performed using Cox proportional hazards regression. Unadjusted and adjusted effect estimates are presented. Multivariate models are adjusted for age, sex, smoking status, cardiovascular disease, stroke, diabetes, asthma, depression, MRC dyspnoea score and *P. aeruginosa* infection. All analyses utilised SPSS version 27 (IBM, USA) or Graphpad Prism version 9 (San Diego, California, USA).

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Results

16963 patients were included in the analysis. 4324 patients had a clinician reported diagnosis of COPD. These patients were initially compared to 12639 patients without a clinician reported diagnosis of COPD. The baseline characteristics of both populations on entry to the registry are shown in table 1. Patients with COPD were older, more likely to be male, had a higher BMI, more co-morbidities, higher MRC dyspnoea score and worse lung function. Inhaled medications, long term oxygen, non-invasive ventilation and macrolide use were all more common in clinician assigned COPD patients while airway clearance and inhaled antibiotics were less commonly used (table S1 online).

Pseudomonas aeruginosa infection was present in 850 (19.7%) patients with clinician assigned COPD associated bronchiectasis and 2197 (17.4%) of patients without clinician assigned COPD. Patients with clinician assigned COPD were also more likely to be infected with *M. catarrhalis,* enteric Gram negative organisms, *S. pneumoniae* and *S. maltophilia* but less likely to have *S. aureus*. Most differences were small and could be explained by more patients with clinician assigned COPD having microbiological testing (table 1). A comparison of the radiological location of bronchiectasis (table S2) showed that clinician assigned COPD associated disease was less likely to affect the middle lobe and lingula and was more likely to affect the lower lobes. Cystic bronchiectasis was evident in 530 (12.3%) of clinician assigned COPD patients and 1839 (14.6%) of non-COPD patients.

COPD was classified as the underlying cause of bronchiectasis by the investigator in 1367 cases (8.1% of all cases).

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COPD and disease severity

Among patients with clinician reported COPD, there was a clear relationship between COPD diagnosis and bronchiectasis severity. Patients with clinician assigned COPD+bronchiectasis had a higher bronchiectasis severity index ($p<0.0001$, figure 1A), a lower QOL-B symptom score indicating worse symptoms (figure 1B), with radiological severity that was slightly higher in the non-COPD group using the Reiff score ($p=0.0001$, figure 1C). A higher proportion of patients with clinician assigned COPD had frequent exacerbations (figure 1D) and hospitalizations for severe exacerbations (figure 1E), clinician assigned COPD patients had a higher rate of prior exacerbations (incidence rate ratio- IRR 1.41 95%CI 1.35-1.47) and a higher rate of prior severe exacerbations (IRR 2.16 95%CI 2.04-2.28, figure 1F).

Clinician reported COPD diagnosis and objective criteria

We observed a disconnect between clinician diagnosis of COPD and the objective ROSE criteria.

3832/4324 (88.6%) patients with a diagnosis of COPD and 11369/12639 (89.9%) patients without a diagnosis of COPD had complete lung function and pack year smoking data available for analysis. These analyses are therefore based on 15231 patients' data.

We observed marked overdiagnosis of COPD using the ROSE criteria. Only 2986 (77.9%) of patients with a diagnosis of COPD had an FEV1/FVC ratio <0.7. 2652 (69.2%) with clinician assigned COPD had a smoking history of 10 or more pack years. Combining these two parameters the proportion meeting the ROSE criteria for "true COPD" among those with a label of COPD was 2130 (55.6%) using the fixed FEV1/FVC ratio, table 2. Thus, only approximately half of patients with a diagnosis of COPD meet the objective definition based on exposure and airflow obstruction (table 2). Airflow obstruction was common in patients without reported COPD. 877 (7.7%) of patients without a clinician diagnosis of COPD met the objective definition.

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Diagnosis of COPD

Using the ROSE criteria we divided the patients into 4 categories- patients with a clinician reported diagnosis of COPD who met the ROSE criteria, those with a report diagnosis of COPD who did not meet the ROSE criteria (either due to lack of airflow obstruction or smoking history), patients who did not have clinician reported COPD but who met the ROSE criteria (indicating possible unrecognised COPD- bronchiectasis association) and those who had neither a COPD diagnosis nor the ROSE criteria. The characteristics of these four groups of patients are shown in table 3.

Patients with clinician diagnosed COPD who did and did not meet ROSE criteria were remarkably similar in terms of age, co-morbidities, sputum volume, dyspnoea and treatments. They differed in terms of worse FEV1 in the “confirmed COPD” group meeting the ROSE criteria and in smoking history, the two features that define these two groups.

The population who met ROSE criteria but were not clinically suspected to have COPD had fewer co-morbidities except for greater asthma and rhinosinusitis compared to the two groups with a reported COPD diagnosis. They had better lung function and less dyspnoea. The group without ROSE criteria and without a COPD diagnosis were younger, more likely to be female, less co-morbid and overall, a very different group in almost every parameter (table 3).

Diagnosis of COPD by country

We investigated whether under or overdiagnosis of COPD associated bronchiectasis may vary by country. This is shown in Figure S1. The data showed a higher frequency of COPD using either

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clinician reported or objective criteria in Eastern European countries with the lowest proportions of patients without COPD (diagnosed or objectively reported) in Macedonia, Poland, Serbia, Romania and Ukraine.

Clinically and objectively confirmed COPD was most common in Macedonia (57.1%), Serbia (36.7%), Switzerland (28.3%) and Poland (27.8%). The clinician diagnosis of COPD in the absence of ROSE criteria which may be taken as a proxy of overdiagnosis of COPD was most common in Romania (40.3%), Ukraine (32.0%) and Macedonia (22.9%). The reporting of no COPD in the presence of ROSE criteria (which can be considered a proxy of underdiagnosis of COPD) was most frequent in Denmark (18.2%), Poland (11.3%) and Slovenia (10.7%). (Figure S1). The percentages of COPD subjects were very similar in the 5 largest countries contributing to the registry (UK, Spain, Italy, Germany and France) and analysis limited to these countries showed similar differences in characteristics between groups (not shown).

Sensitivity analysis: postbronchodilator spirometry

6206 patients had post-bronchodilator spirometry data available. In a sensitivity analysis limited to only patients who had post-bronchodilator spirometry available at baseline, 1087 (17.5%) had clinician diagnosed COPD and met ROSE criteria, 649 (10.5%) had a clinical diagnosis of COPD and did not meet ROSE criteria, 371 (6.0%) had no clinical diagnosis of COPD but met ROSE criteria and 4099 (66.0%) were not diagnosed with COPD and did not meet ROSE criteria. These proportions are very similar to those observed in the overall population.

COPD and Long Term Clinical Outcomes

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Table 4 shows the effect estimates for each definition of COPD for the outcomes of exacerbations, severe exacerbations requiring hospitalization and mortality during follow-up. For the mortality analysis the median length of follow-up per individual was 1141 days (3 years) with interquartile range 786 days (2 years) to 1611 days (4 years). There were 31850 exacerbations and 5991 hospitalizations recorded during the follow-up period with 1024 recorded deaths.

Clinical outcomes were clearly worse for individuals with clinician diagnosed COPD. Table 4 shows the markedly increased mortality and hospitalization risk with a lesser but still significant increase in exacerbations. These effect estimates remained significant after adjustment for confounders.

Interestingly the risk of mortality both unadjusted and adjusted were similar when patients with a clinician diagnosis of COPD were divided into those with and without ROSE criteria, although those meeting ROSE criteria were overall higher. Similarly, the risk of hospitalization and exacerbations were also similarly increased. Patients who met the ROSE criteria but did not carry a clinical label of COPD had much better outcomes than even patients with clinician diagnosed COPD that did not meet ROSE criteria. These patients did not have increased mortality or exacerbations compared to patients without clinician assigned COPD and without ROSE criteria but did show an increase in severe exacerbations even after multivariable adjustment.

Discussion

The association between bronchiectasis and COPD is an important clinical challenge and management strategies for this population are currently unclear.[2,3,17,18] Most studies conducted into this association have shown worse clinical outcomes in patients that carry both labels, compared to patients that have either disease alone.[4,19] The definitions of these conditions are based on

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radiology, physiology and exposure to tobacco smoke or other environmental risk factors. As bronchiectasis can be associated with airflow obstruction[20], as well as other features associated with COPD such as emphysema[21], without exposure to tobacco smoke, there is a risk that COPD will be over or underdiagnosed in bronchiectasis patients leading to inappropriate treatment and sometimes stigma.[22]

Our data, in the world's largest prospective cohort of patients with bronchiectasis, supports several important conclusions. First, patients with bronchiectasis who carry a label of COPD made by a clinician have worse clinical outcomes compared to those without, mirroring the results of previous smaller studies. Patients have increased mortality, and higher risk of hospitalization and exacerbations. Patients also have worse quality of life and respiratory symptoms.

Nevertheless, we found that 21.7% of patients with a clinical diagnosis of COPD had never smoked and only 77.8% had evidence of airflow obstruction on spirometry. Overall, nearly half (44.4%) of patients with a clinical diagnosis of COPD therefore did not meet the ROSE criteria for COPD in association with bronchiectasis. Interestingly we also identified patients with a history of smoking and airflow obstruction without a diagnosis of COPD. These patients were less common (7.7% of the patients without a COPD diagnosis) and tended to have less severe airflow obstruction (mean ratio 61.8%). This suggests a subset of patients with milder airflow obstruction and a history of smoking have not been given a diagnosis of COPD. Patients with asthma were over-represented in this group and so it should be acknowledged that this may account for some chronic airflow obstruction in this group. Nevertheless, these data are consistent with the wider context of COPD outside bronchiectasis where over and underdiagnosis are common. Quality-assured post-bronchodilator spirometry and an appropriate clinical history is the only way to make or exclude a diagnosis of COPD.

Our results suggest that the label of COPD is widely used inappropriately in the bronchiectasis patient population. This has important implications since COPD is treated differently to

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bronchiectasis, and overuse of inhaled corticosteroids and bronchodilators has been documented in bronchiectasis.[23,24] Most bronchiectasis clinical studies exclude patients with underlying COPD and our observations suggest a high proportion of patients with a diagnosis of COPD should in fact be eligible for bronchiectasis trials.[25,26] We observed similar rates of COPD across countries, with more COPD diagnoses in Eastern Europe consistent with a higher prevalence of cigarette smoking in this region.[27] Over and under-diagnosis of COPD also appeared to be higher in Eastern European countries. Our report of baseline data from the registry identified a lower standard of care in Eastern Europe and the data reported here suggest this extends to accuracy of diagnosis.[12]

Using the ROSE criteria our estimate of the prevalence of COPD associated with bronchiectasis is 19.9%. An important limitation of the data available in the EMBARC registry is the absence of comprehensive exposure data other than cigarette smoking. It is therefore possible that some cases of non-smoking COPD are not captured in our “ROSE +” group. Nevertheless while it is possible that some patients have exposures other than smoking to explain airflow obstruction, in the presence of bronchiectasis, the vicious cycle of inflammation associated with bronchiectasis may be a more likely cause of airflow obstruction than passive cigarette exposure, pollution or biomass exposure. In addition it is documented that airflow obstruction can be intermittent, with some patients without airflow obstruction on spirometry at one time point having obstruction at other timepoints.[28] It is possible therefore that some patients had airflow obstruction at one timepoint in the past. For all of these reasons while the ROSE criteria may be superior to objective clinical judgement in defining this clinical entity, no criteria are perfect and therefore our data can only be considered estimates of the true rate of under and overdiagnosis.

The other key finding of our study relates to clinical outcomes. Patients with a clinical label of COPD had universally worse outcomes including mortality and exacerbations. Intriguingly, however, this was true whether or not patients had airflow obstruction and whether or not patients had a history of cigarette smoking. The characteristics of the patient populations meeting the ROSE definition and

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not meeting the ROSE definition[3] were very similar other than their smoking history and presence of airflow obstruction. One possible conclusion of this data is that clinicians give the label of COPD to patients with more severe disease, including patients with severe breathlessness, or requiring particular therapies such as oxygen, regardless of the presence of a smoking history or airflow obstruction. That the poor outcomes are multifactorial rather than being entirely related to smoking and airflow obstruction is reflected in the relatively "benign" outcomes seen with patients who have no label of COPD but meet the criteria for COPD based on airflow obstruction and smoking history.

A limitation of our analysis is that most spirometry in the cohort was pre-bronchodilator, as this is an observational registry of lung function performed in clinical practice. We therefore cannot confirm if some cases of airflow obstruction would have reversed with bronchodilator treatment. Since this would tend to reduce the proportion of patients with "true" COPD, we do not believe this affects the primary conclusions of the study, indeed the extent of overdiagnosis of COPD in this population may be greater if postbronchodilator spirometry was routinely applied. A sensitivity analysis limited to post-bronchodilator spirometry confirmed the conclusions of the study. Other limitations are intrinsic to a real-life registry, including that microbiological sampling was only performed when clinically indicated.

Our study supports the need for the use of objective criteria in defining bronchiectasis and COPD association. The proposed ROSE criteria, if applied more widely would help to reduce variation in the use of the term COPD and its application to bronchiectasis patients without appropriate exposures or airflow obstruction.

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Tables

Variables	Bronchiectasis +COPD	Bronchiectasis alone	p-value
n.	4324	12639	
Demographics			
Median (IQR) age, years	70 (63-76)	66 (54-73)	<0.0001
Male, n (%)	2431 (56.2%)	4197 (33.2%)	<0.0001
Median (IQR) BMI, kg/m^2	25.4 (22.2-29.3)	24.7 (21.6-28.4)	<0.0001
Never smokers, n (%)	890 (20.6%)	8206 (64.9%)	<0.0001
Ex smokers, n (%)	2834 (65.5%)	3951 (31.3%)	<0.0001
Current smokers, n (%)	600 (13.9%)	482 (3.8%)	<0.00001
Comorbidity			
Cardiovascular disorders, n (%)	2026 (46.9%)	3483 (27.6%)	<0.0001
Stroke, n (%)	241 (5.6%)	359 (2.8%)	<0.0001
Diabetes, n (%)	642 (14.8%)	1082 (8.6%)	<0.0001
Rhinosinusitis, n (%)	597 (13.8%)	2880 (22.8%)	<0.0001
Asthma, n (%)	1165 (26.9%)	4102 (32.5%)	<0.0001
Osteoporosis, n (%)	707 (16.4%)	1521 (12.0%)	<0.0001
Depression, n (%)	793 (18.3%)	1584 (12.5%)	<0.0001
Solid tumour, n (%)	551 (12.7%)	1312 (10.4%)	<0.0001
Lung Function			
FEV1 Litres	1.33 (0.95-1.84)	1.93 (1.41-2.51)	<0.0001
FEV1 % predicted	56.5 (40.4-75.7)	83.1 (64.1-100.6)	<0.0001
FVC % predicted	79.9 (64.0-97.5)	94.9 (78.0-110.6)	<0.0001
Clinical status			
Sputum volume ml/day	10 (0-25)	5 (0-20)	<0.0001
MRC dyspnoea score	2 (1-3)	1 (0-2)	<0.0001
Microbiology in sputum at baseline			
P.aeruginosa	850 (19.7%)	2197 (17.4%)	<0.0001
H. Influenzae	749 (17.4%)	2117 (16.8%)	0.39
M. catarrhalis	219 (5.1%)	433 (3.4%)	<0.0001

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Enterobacteriaceae	609 (14.1%)	1320 (10.5%)	<0.0001
S. aureus	218 (5.1%)	826 (6.5%)	<0.0001
S. pneumoniae	304 (7.0%)	728 (5.8%)	0.003
S. maltophilia	95 (2.2%)	221 (1.8%)	0.06
No sputum sample sent in stable state	1741 (40.4%)	5763 (45.6%)	<0.0001

Table 1. Patient characteristics according to baseline COPD status.

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	Reported COPD	No reported COPD
N	4324	12639
N with complete lung function data	3832 (88.6%)	11369 (90.0%)
FEV1/FVC ratio <0.7	2986 (77.9%)	4694 (41.3%)
10 or more pack year smoking history	2652 (69.2%)	2241 (19.7%)
ROSE criteria (Fixed ratio)	2130 (55.6%)	877 (7.7%)

Table 2. COPD diagnosis and objective criteria. Abbreviations FEV1= forced expiratory volume in 1 second, FVC= forced vital capacity.

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Variables	COPD reported and ROSE criteria met (COPD+ROSE+)	COPD reported but no ROSE criteria met (COPD+ROSE-)	No COPD reported but meets ROSE criteria (COPD-ROSE+)	No COPD reported and no criteria met (COPD-ROSE-)
n.	2130	1702	877	10522
Demographics				
Median (IQR) age, years	70 (64-76)	70 (63-76)	69 (60-75)	65 (53-73)
Female, n (%)	743 (34.9%)	899 (52.8%)	404 (46.1%)	1084 (10.3%)
Median (IQR) BMI, kg/m^2	25.3 (22.2-29.1)	25.6 (22.3-29.5)	25.6 (22.5-29.5)	24.2 (21.2-27.9)
Never smokers, n (%)	0 (0%)	770 (45.2%)	0 (0%)	7463 (70.9%)
Ex smokers, n (%)	1738 (81.6%)	785 (46.1%)	775 (88.4%)	2733 (26.0%)
Current smokers, n (%)	392 (18.4%)	147 (8.6%)	102 (11.6%)	326 (3.1%)
Comorbidity				
Cardiovascular disorders, n (%)	1035 (48.6%)	760 (44.7%)	298 (34.0%)	2824 (26.8%)
Stroke, n (%)	124 (5.8%)	87 (5.1%)	38 (4.3%)	276 (2.6%)
Diabetes, n (%)	325 (15.3%)	237 (13.9%)	96 (10.9%)	877 (8.3%)
Rhinosinusitis, n (%)	249 (11.7%)	288 (16.9%)	157 (17.9%)	2531 (24.1%)
Asthma, n (%)	444 (20.8%)	599 (35.2%)	315 (35.9%)	3486 (33.1%)
Osteoporosis, n (%)	306 (14.4%)	321 (18.9%)	100 (11.4%)	1279 (12.2%)
Depression, n (%)	376 (17.7%)	325 (19.1%)	137 (15.6%)	1297 (12.3%)
Solid tumour, n (%)	269 (12.6%)	193 (11.3%)	105 (12.0%)	1057 (10.0%)
Lung Function				
FEV1 Litres	1.20 (0.88-1.65)	1.49 (1.07-2.00)	1.76 (1.30-2.19)	1.95 (1.42-2.54)
FEV1 % predicted	50.0 (36.3-66.4)	66.8 (48.4-84.7)	70.5 (56.9-88.4)	84.1 (84.1-101.2)
FVC % predicted	78.4 (62.8-96.5)	81.3 (65.3-98.0)	94.6 (78.6-111.4)	94.9 (78.0-110.5)
Clinical status				
Sputum volume ml/day	10 (0-25)	10 (0-25)	8 (0-20)	6 (0-20)
MRC dyspnoea score	2 (1-3)	2 (1-3)	1 (0-2)	1 (0-2)
Treatment				
Regular airway clearance, n (%)	1020 (47.9%)	838 (49.2%)	469 (53.5%)	5718 (54.3%)

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Long term macrolide treatment, n (%)	395 (18.5%)	339 (19.9%)	126 (14.4%)	1832 (17.4%)9
Inhaled antibiotic treatment, n (%)	154 (7.2%)	138 (8.1%)	76 (8.7%)	863 (8.2%)
Any antibiotic prophylaxis, n (%)	92 (4.3%)	96 (5.6%)	40 (4.6%)	481 (4.6%)
Inhaled corticosteroids, n (%)	1455 (68.3%)	1061 (62.3%)	469 (53.5%)	4981 (47.3%)
Long-acting beta agonist, n (%)	1581 (74.2%)	1090 (64.0%)	473 (53.9%)	4822 (45.8%)
Long-acting muscarinic antagonist, n (%)	1378 (64.7%)	816 (47.9%)	282 (32.2%)	1890 (18.0%)
Long term oxygen therapy, n (%)	377 (17.7%)	181 (10.6%)	37 (4.2%)	290 (2.8%)
Non-invasive ventilation, n (%)	85 (4.0%)	55 (3.2%)	11 (1.3%)	155 (1.5%)
Oral theophylline, n (%)	145 (6.8%)	77 (4.5%)	21 (2.4%)	193 (1.8%)

Table 3. Characteristics of patients with COPD and without COPD using clinical and objective (ROSE) criteria.

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Group	N		Mortality (HR)	Hospitalizations	Exacerbations
COPD (clinical definition only)	4324	Unadjusted	2.66 (2.36-3.01)	2.74 (2.53-2.97)	1.46 (1.38-1.54)
		Adjusted*	1.93 (1.70-2.19)	2.41 (2.20-2.65)	1.44 (1.35-1.54)
COPD subgroups					
COPD reported and ROSE criteria met (COPD+ROSE+)	2130	Unadjusted	3.24 (2.78-3.79)	3.15 (2.84-3.49)	1.50 (1.39-1.61)
		Adjusted*	2.24 (1.90-2.64)	3.09 (2.70-3.53)	1.55 (1.41-1.69)
COPD reported but no ROSE criteria met (COPD+ROSE-)	1702	Unadjusted	2.46 (2.06-2.95)	2.55 (2.28-2.86)	1.41 (1.30-1.53)
		Adjusted*	1.82 (1.51-2.18)	2.35 (2.08-2.66)	1.40 (1.29-1.53)
No COPD reported but meets ROSE criteria (COPD-ROSE+)	877	Unadjusted	1.69 (1.27-2.24)	1.47 (1.23-1.75)	1.13 (1.01-1.27)
		Adjusted*	1.33 (0.99-1.78)	1.46 (1.20-1.78)	1.17 (1.03-1.32)
No COPD reported and no criteria met (COPD-ROSE-)	10522	Unadjusted	1.00 (reference)	1.00 (reference)	1.00 (reference)
		Adjusted*	1.00 (reference)	1.00 (reference)	1.00 (reference)

Table 4. Effect estimates for clinical outcomes based on different COPD definitions *Adjusted for age, sex, smoking status, cardiovascular disease, stroke, diabetes, asthma, depression, MRC dyspnoea score*, *P. aeruginosa* infection.

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Figure Legend

Figure 1. Severity of disease and its association with clinician assigned COPD A: Bronchiectasis severity index B: Quality of life bronchiectasis respiratory symptom score C: Reiff score D: Exacerbation frequency E: Hospitalization for severe exacerbations F: Negative binomial regression model for prior exacerbations and severe exacerbations resulting in hospital admissions. Incidence rate ratios are shown compared to the reference group which was patients without clinician diagnosed COPD. All comparisons shown in the figure $p<0.0001$ with the exception of radiological severity ($p=0.0001$).

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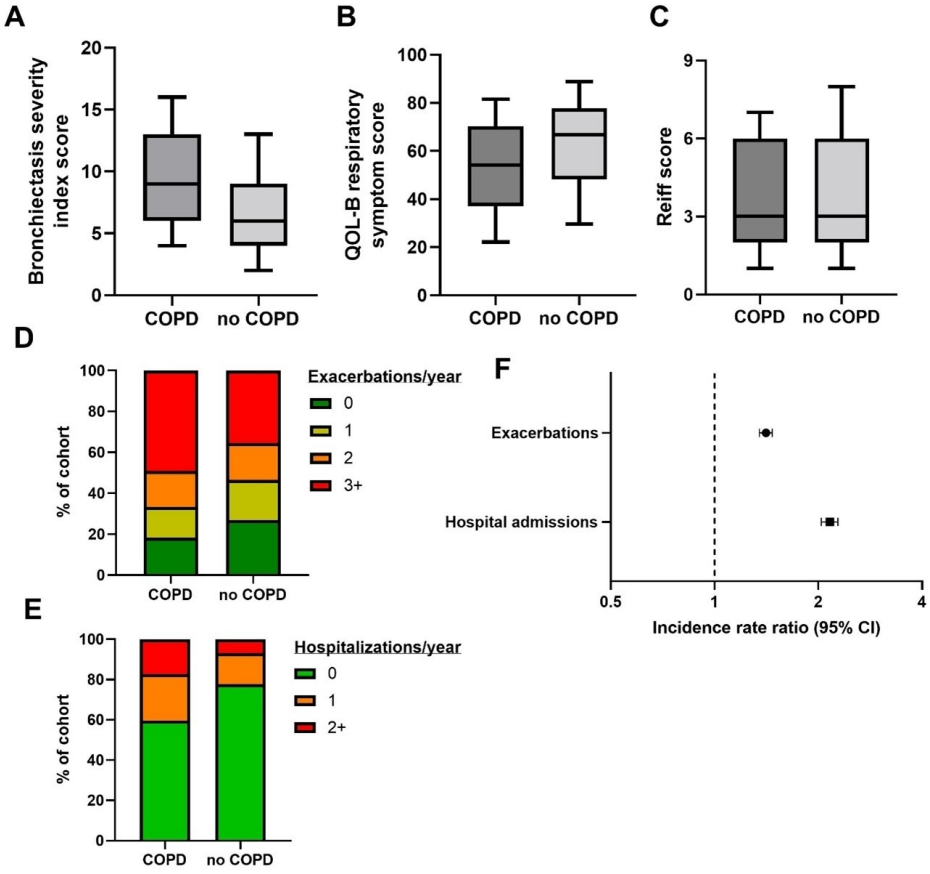

Figure 1. Severity of disease and its association with clinician assigned COPD A: Bronchiectasis severity index B: Quality of life bronchiectasis respiratory symptom score C: Reiff score D: Exacerbation frequency E: Hospitalization for severe exacerbations F: Negative binomial regression model for prior exacerbations and severe exacerbations resulting in hospital admissions. Incidence rate ratios are shown compared to the reference group which was patients without clinician diagnosed COPD. All comparisons shown in the figure $p<0.0001$ with the exception of radiological severity ($p=0.0001$).

159x149mm (220 x 220 DPI)

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The Association Between Bronchiectasis and Chronic Obstructive Pulmonary Disease: Data from the European Bronchiectasis Registry (EMBARC)

Eva Polverino, Anthony De Soyza, Katerina Dimakou, Letizia Traversi, Apostolos Bossios, Megan L Crichton, Felix C Ringshausen, Montserrat Vendrell, Pierre-Régis Burgel, Charles S Haworth, Michael R Loebinger, Natalie Lorent, Isabell Pink, Melissa McDonnell, Sabina Skrgat, Luis M Carro, Oriol Sibila, Menno van der Eerden, Paula Kauppi, Amelia Shoemark, Adelina Amorim, Jeremy S Brown, John R Hurst, Marc Miravitlles, Rosario Menendez, Antoni Torres, Tobias Welte, Francesco Blasi, Josje Altenburg, Michal Shteinberg, Wim Boersma, Stuart J Elborn, Pieter C Goeminne, Stefano Aliberti, James D Chalmers On behalf of the EMBARC registry investigators.

ONLINE DATA SUPPLEMENT

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Variables		Bronchiectasis +COPD	Bronchiectasis alone	p-value
n.		4324	12639	
Demographics				
Median (IQR) age, years		70 (63-76)	66 (54-73)	<0.0001
Male, n (%)		2431 (56.2%)	4197 (33.2%)	<0.0001
Median (IQR) BMI, kg/m^2		25.4 (22.2-29.3)	24.7 (21.6-28.4)	<0.0001
Never smokers, n (%)		890 (20.6%)	8206 (64.9%)	<0.0001
Ex smokers, n (%)		2834 (65.5%)	3951 (31.3%)	<0.0001
Current smokers, n (%)		600 (13.9%)	482 (3.8%)	<0.00001
Comorbidity				
Cardiovascular disorders, n (%)		2026 (46.9%)	3483 (27.6%)	<0.0001
Stroke, n (%)		241 (5.6%)	359 (2.8%)	<0.0001
Diabetes, n (%)		642 (14.8%)	1082 (8.6%)	<0.0001
Liver disease, n (%)		37 (0.9%)	66 (0.5%)	0.022
Chronic renal failure, n (%)		230 (5.3%)	437 (3.5%)	<0.0001
Rhinosinusitis, n (%)		597 (13.8%)	2880 (22.8%)	<0.0001
Asthma, n (%)		1165 (26.9%)	4102 (32.5%)	<0.0001
Osteoporosis, n (%)		707 (16.4%)	1521 (12.0%)	<0.0001
Depression, n (%)		793 (18.3%)	1584 (12.5%)	<0.0001
Solid tumour, n (%)		551 (12.7%)	1312 (10.4%)	<0.0001
Lung Function				
FEV1 Litres		1.33 (0.95-1.84)	1.93 (1.41-2.51)	<0.0001
FEV1 % predicted		56.5 (40.4-75.7)	83.1 (64.1-100.6)	<0.0001
FVC Litres		2.40 (1.85-3.10)	2.73 (2.13-3.43)	<0.0001
FVC % predicted		79.9 (64.0-97.5)	94.9 (78.0-110.6)	<0.0001
FEV1/FVC ratio		58.0 (46.5-68.6)	72.5 (63.8-79.3)	<0.0001
Clinical status				
Sputum volume ml/day		10 (0-25)	5 (0-20)	<0.0001
MRC, n (%)	0	400 (9.3%)	4031 (31.9%)	<0.0001
	1	1120 (25.9%)	4441 (35.1%)	

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	2	1204 (27.8%)	2451 (19.4%)	
	3	1021 (23.6%)	1170 (9.3%)	
	4	538 (12.4%)	352 (2.8%)	
Microbiology				
P.aeruginosa		850 (19.7%)	2197 (17.4%)	<0.0001
H. Influenzae		749 (17.4%)	2117 (16.8%)	0.39
M. catarrhalis		219 (5.1%)	433 (3.4%)	<0.0001
Enterobacteriaceae		609 (14.1%)	1320 (10.5%)	<0.0001
S. aureus		218 (5.1%)	826 (6.5%)	<0.0001
S. pneumoniae		304 (7.0%)	728 (5.8%)	0.003
S. maltophilia		95 (2.2%)	221 (1.8%)	0.06
No sputum sample sent in stable state		1741 (40.4%)	5763 (45.6%)	<0.0001
Treatment				
Regular airway clearance, n (%)		2072 (47.9%)	6667 (52.7%)	<0.0001
Long term macrolide treatment, n (%)		821 (19.0%)	2119 (16.8%)	<0.0001
Inhaled antibiotic treatment, n (%)		314 (7.3%)	996 (7.9%)	0.19
Other oral antibiotic prophylaxis, n (%)		215 (5.0%)	579 (4.6%)	0.50
Inhaled corticosteroids, n (%)		2805 (64.9%)	5895 (46.6%)	<0.0001
Long-acting beta agonist, n (%)		2942 (68.0%)	5690 (45.0%)	<0.0001
Long-acting muscarinic antagonist, n (%)		2392 (55.3%)	2315 (18.3%)	<0.0001
Long term oxygen therapy, n (%)		635 (14.7%)	365 (2.9%)	<0.0001
Non-invasive ventilation, n (%)		163 (3.8%)	187 (1.5%)	<0.0001
Oral theophylline, n (%)		247 (5.7%)	236 (1.9%)	<0.0001

Table S1. Characteristics of patients with COPD in association with bronchiectasis compared to patients without reported COPD.

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		COPD	No COPD
RUL	Affected	1614 (37.3%)	5003 (39.6%)
	Cystic	187 (4.3%)	665 (5.3%)
RML	Affected	2381 (55.0%)	7705 (61.0%)
	Cystic	219 (5.1%)	884 (7.0%)
RLL	Affected	3251 (75.1%)	8687 (68.8%)
	Cystic	280 (6.5%)	938 (7.4%)
LUL	Affected	1412 (32.6%)	4262 (33.7%)
	Cystic	157 (3.6%)	526 (4.2%)
Lingula	Affected	1867 (43.1%)	6185 (49.0%)
	Cystic	178 (4.1%)	652 (5.2%)
LLL	Affected	3139 (72.5%)	8762 (69.4%)
	Cystic	293 (6.8%)	1036 (8.2%)
Reiff score	Median(IQR)	3 (2-6)	3 (2-6)

Table S2. Radiological characteristics of disease in patients with and without co-existing COPD.

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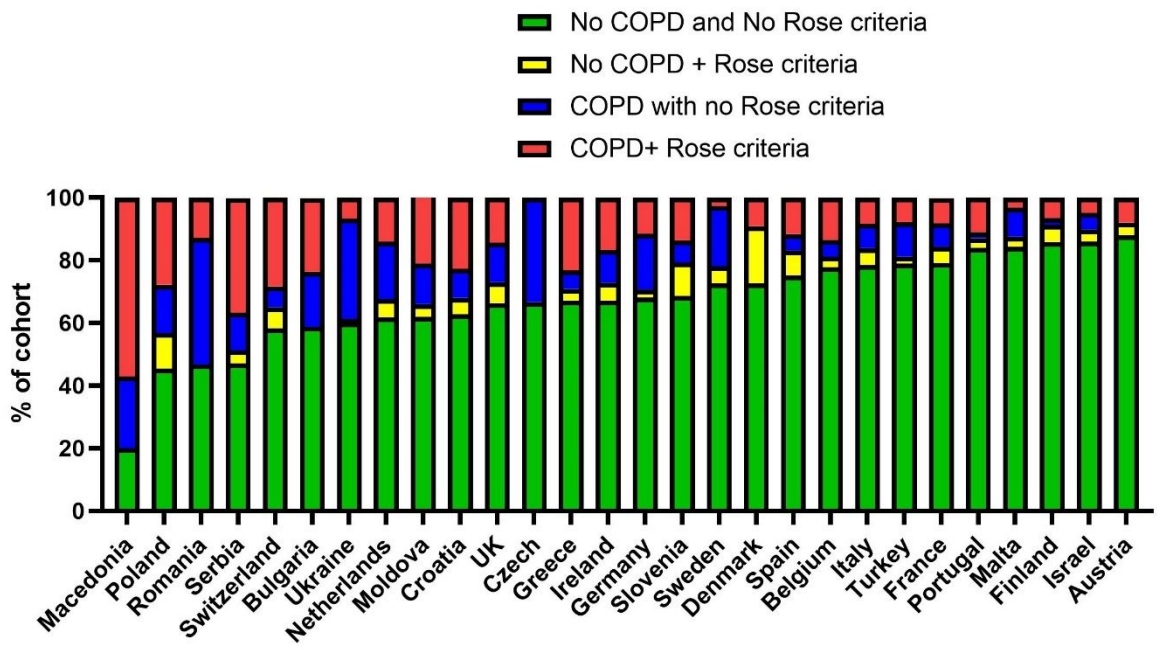

Figure S1. The frequency of different criteria for COPD diagnosis in 28 countries included in the EMBARC registry. The data are sorted left to right based on the lowest (left) to highest (right) proportion of patients without either reported or objective COPD (green bars).

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