



## Early View

Original research article

# **ROSE: Radiology, Obstruction, Symptoms and Exposure, a Delphi consensus definition of the association of COPD and Bronchiectasis by the EMBARC Airways Working Group**

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**ROSE: Radiology, Obstruction, Symptoms and Exposure, a Delphi consensus definition of the association of COPD and Bronchiectasis by the EMBARC Airways Working Group**

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## **Abstract**

**INTRODUCTION:** The coexistence of chronic obstructive pulmonary disease (COPD) and bronchiectasis (BE) seems to be common and associated with a worse prognosis than for either disease individually. However, no definition of this association exists to guide researchers and clinicians.

**METHODS:** We conducted a Delphi survey involving expert pulmonologists and radiologists from Europe, Turkey and Israel in order to define the 'COPD-BE association'.

A panel of 16 experts from EMBARC selected 35 statements for the survey after reviewing scientific literature. Invited participants, selected on the basis of expertise, geographical and gender distribution, were asked to express agreement on the statements. Consensus was defined as a score of  $\geq 6$  points (scale 0 to 9) in  $\geq 70\%$  of answers across two scoring rounds.

**RESULTS:** A-hundred-and-two (72.3%) out of 141 invited experts participated the first round. Their response rate in the second round was 81%. The final consensus definition of 'COPD-BE association' was: "The coexistence of (1) specific radiological findings (*abnormal bronchial dilatation, airways visible within 1cm of pleura and/or lack of tapering sign* in  $\geq 1$  pulmonary segment and in  $>1$  lobe) with (2) an obstructive pattern on spirometry ( $FEV_1/FVC < 0.7$ ), (3) at least two characteristic symptoms (*cough, expectoration, dyspnoea, fatigue, frequent infections*) and (4) current or past exposure to smoke ( $\geq 10$  pack-years) or other toxic agents (*biomass, etc.*)". These criteria form the acronym "ROSE" (Radiology, Obstruction, Symptoms, Exposure).

**CONCLUSIONS:** The Delphi process formulated a European consensus definition of 'COPD-BE association'. We hope this definition will have broad applicability across clinical practice and research in the future.

**Keywords:** COPD-Bronchiectasis association, definition, Delphi, ROSE

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) and bronchiectasis (BE) are two of the most frequent chronic respiratory diseases, both representing important causes of morbidity and mortality, as well as increasing burden for healthcare systems worldwide[1, 2]. The definition of COPD is established by the Global Initiative for Obstructive Lung Disease (GOLD) as “a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases [3].” Recently, an international study group involving experts from Europe (EMBARC) and the USA has generated the first consensus definition of “clinically significant BE”, including specific clinical signs/symptoms and radiological findings (‘Consensus definitions of bronchiectasis for use in clinical trials’, submitted).

Although these two entities individually have very different characteristics, the presence of BE and COPD in the same patient is quite frequent. [4–6]. In fact, while usual clinical presentation of COPD is mostly driven by dyspnoea and cough[3], in BE chronic expectoration and recurrent respiratory infections are the most frequent manifestations[7]. In presence of compatible symptoms, the diagnostic process is also different, since in COPD is based on a functional assessment (airflow limitation after bronchodilatation), in BE it is based on a radiological evaluation (specific findings on computed tomography (CT) scan)[3, 7]. Additionally, risk factors are different: the exposure to smoke or other irritants is deemed necessary to confirm diagnosis of COPD, while in BE they are less clear and extremely heterogeneous depending on patient’ age and comorbidities. Some specific conditions, such as primary immunodeficiencies[8], gastro-oesophageal reflux[9] or lung tuberculous or non-tuberculous mycobacteria (NTM) infections[10], have been described as risk factors for developing BE. Additionally, severe chronic asthma[11] or COPD[12] are also considered risk factors to develop secondary BE. As a consequence, the epidemiology of COPD and BE may be very different depending on risk factors and other elements such as quality of access to health care (spirometry, CT scan, among others)[10, 13, 14].

The epidemiology of the association between COPD and BE is even less clear. In fact, the reported prevalence of BE in COPD patients varies considerably across series, from 4% to 75%[4, 15–17]. Different factors can be invoked to understand such variability in prevalence rates: series differ in inclusion criteria, severity of disease, definition of bronchiectasis and method used for radiological diagnosis. Moreover, the presence of increased vessel size (such as in pulmonary hypertension), affecting the broncho-arterial (BA) ratio, could be a cause of under-

diagnosis when the BA ratio is used as diagnostic criteria on high-resolution computed tomography (HRCT)[18]. More commonly however, BE may be overdiagnosed, as bronchial dilatation may be found in 10-30% of CT scans of healthy and asymptomatic subjects over 40 years of age[19, 20]. Also, the presence of hypoxic vasoconstriction, frequent in chronic pulmonary diseases, could contribute to BE overdiagnosis[16]. This variability in BA ratio and its interpretation may influence the diagnosis of BE, and, even more frequently, in COPD patients [8].

Across the limited number of BE studies where the prevalence of COPD has been reported, it has ranged between 8.8% and 32%[12, 20–23]. In these studies, in the absence of an established definition of COPD-BE association, the diagnosis of COPD was based on a functional obstructive pattern and, in some cases, smoking history.

Regardless of the primary diagnosis, the co-existence of COPD and BE is usually associated with greater symptom burden, greater frequency and severity of exacerbations, more severe airways obstruction and increased mortality risk compared with any of the two diseases alone[17, 24, 25]. Due to all these reasons, an international group of experts has worked towards achieving a consensus definition of the association of COPD and BE independently of the primary diagnosis. Such a definition will allow, first, a standardised epidemiological data collection and, second, to assess the health-economic burden of this association. Moreover, a consensus definition could be a critical tool to better select patients for future clinical trials.

## **METHODS**

### **Design of the study**

This was a Delphi survey with the objective of developing an international consensus definition of the COPD-BE association.

Delphi is a consensus method developed to measure levels of agreement between experts on a subject where scientific evidence is lacking, limited or contradictory[26]. The Delphi method is based on four characteristics: (1) anonymity: guaranteed by the centralization of questionnaire answers by a single moderator; (2) iteration: meaning that same questions are reiterated in successive rounds until reaching stability in answers; (3) controlled feedback: participants are provided a feedback of previous rounds before proceeding with the following ones. The moderator can usually decide how much information will be provided after each round and the means by which this is delivered; (4) statistical “group response”, usually measured with central tendency, dispersion and frequency distributions[27–29].

Additionally, this method allows the collection of numerous expert opinions without the need of face-to face meetings. Methods were repeatedly discussed within the panel in order to enhance validity and avoid methodological biases.

In our Delphi, a panel of experts selected the statements to be graded by survey respondents, in order to describe the association between COPD and BE. The items receiving the highest level of concordance after 2 rounds were selected as the criteria forming the final definition.

### **Participants in the survey**

The Delphi survey was designed by a panel of 16 experts in COPD and BE from the EMBARC Airways Working Group, including a small group of radiologists with specialised interest in thoracic imaging.

The panel selected participants trying to ensure a diverse distribution by gender, geography and expertise (for COPD, BE or both and thoracic radiology) in order to obtain a solid representation of opinions while respecting Delphi method recommendations[26–29]. We planned a target of 100 responses; therefore, assuming a ~20% of non-responders, a total of 125 invitations were sent to accredited experts in the fields of COPD, bronchiectasis and thoracic radiology from European countries, Turkey and Israel, selected based on published literature in the field. A pool of radiologists (20% of total invitations) was included due to the important role played by radiology in the diagnosis of BE. Moreover, the 16 members of the panel were also invited to complete the survey.

### **Development of the survey**

Initially, the panel performed a scoping review of literature regarding the association of COPD and BE and discussed the findings, identifying crucial issues and common points in prior studies related to the association. After setting the aim of the definition, each panellist proposed statements for internal discussion. From the original list, the panel formulated a short list of 35 statements split into 5 categories: clinical, functional, microbiological, radiological and pathophysiological features (Table 1).

**TABLE 1. FINAL LIST OF STATEMENTS INCLUDED IN THE DELPHI SURVEY. PARTICIPANTS WERE ASKED TO GRADE EACH ITEM, ACCORDING TO THEIR LEVEL OF AGREEMENT ON THE NECESSITY FOR THE STATEMENT TO BE PART OF THE COPD-BE ASSOCIATION DEFINITION.**

**CLINICAL ITEMS REQUIRED TO DEFINE THE ASSOCIATION OF COPD AND BRONCHIECTASIS**

1. Age > 35 years old
2. Current or past smoking habit ( $\geq 10$  pack-years) or other toxic exposure (biomass, industrial etc.)
3. Presence of at least 15ml of expectorated sputum most of the days
4. Presence of purulent sputum most of the days
5. Presence of haemoptysis
6. Presence of chronic cough and expectoration for at least 3 consecutive months in the last two years
7. Presence of dyspnoea (mMRC $\geq 1$ ) in the last two years
8. History of at least 1 exacerbation in the previous year
9. History of frequent infectious exacerbations ( $\geq 2$ )
10. History of at least 1 severe exacerbation in the last year (hospitalization or intravenous antibiotic therapy)

**RADIOLOGICAL ITEMS REQUIRED TO DEFINE THE ASSOCIATION OF COPD AND BRONCHIECTASIS:**

11. Lack of airway tapering sign
12. Airways visible within 1cm of the pleural surface
13. BE (bronchial dilatation) in at least one pulmonary segment in one lobe
14. BE (bronchial dilatation) in more than one pulmonary segment in one lobe
15. BE (bronchial dilatation) in one or more pulmonary segments in more than one lobe
16. Presence of extensive emphysema
17. Extensive bronchial wall thickening

|  |   |
|--|---|
|  | 18. Presence of diffuse mucus plugging  |
|  | 19. Presence of air trapping  |
| <b>FUNCTIONAL ITEMS REQUIRED TO DEFINE THE ASSOCIATION OF COPD AND BRONCHIECTASIS:</b>         |   |
|  | 20. Post-bronchodilator FEV1/FVC<0.7  |
|  | 21. Post-bronchodilator FEV1/FVC< LLN   |
|  | 22. A positive BD test excludes the diagnosis of COPD-BE association                        |
|  | 23. A mixed (restrictive/obstructive) pattern excludes the diagnosis of COPD-BE association |
|  | 24. A history of positive BD test excludes the diagnosis of COPD-BE overlap                 |
|  | 25. A documented history of asthma excludes the diagnosis of COPD-BE overlap                |
| <b>MICROBIOLOGICAL ITEMS REQUIRED TO DEFINE THE ASSOCIATION OF COPD AND BRONCHIECTASIS:</b>    |   |
|  | 26. At least one isolation of PPM in sputum in the last year in steady state                |
|  | 27. >1 isolation of PPM in sputum in the last year in steady state                          |
|  | 28. History of chronic bronchial infection by any PPM in steady state                       |
|  | 29. Isolation of <i>Pseudomonas aeruginosa</i> in sputum                                    |
|  | 30. No isolation of PPM   |
| <b>PATHOPHYSIOLOGICAL ITEMS REQUIRED TO DEFINE THE ASSOCIATION OF COPD AND BRONCHIECTASIS:</b> |   |
|  | 31. Blood leucocytosis in stable clinical conditions  |
|  | 32. High blood level of C-reactive protein in stable clinical conditions                    |
|  | 33. High blood level of fibrinogen in stable clinical conditions                            |
|  | 34. High neutrophil count in sputum in stable clinical conditions                           |

35. High eosinophil count in serum in stable clinical conditions

Abbreviations. mMRC: modified Medical Research Council; BE: bronchiectasis; FEV1: Forced Expiratory Volume in the 1st second; FVC: Forced Vital Capacity; LLN: Lower Limit of Normal; BD: Bronchodilation; COPD: Chronic Obstructive Pulmonary Disease; PPM: Potential Pathogenic Microorganisms

## **Elaboration of consensus definition**

Participants were invited to grade the selected statements from 0 (completely disagree) to 9 (fully agree). Radiologists were asked to only complete the Radiology section of the survey, while clinicians completed all sections.

After the first round, the panel defined consensus as the scoring of at least 6 points (positive consensus) or fewer than 4 points (negative consensus) in  $\geq 70\%$  of the responders, according to Delphi methodology [20]. Furthermore, after the analysis of results from the first round, the second round was designed where some questions were reiterated, some were reformulated to improve clarity and some new questions were added to enhance the quality of the definition.

Finally, the panel formulated the consensus definition with the criteria that reached the higher level of consensus at the end of the second round.

## **RESULTS (587 words)**

### **a. FIRST ROUND**

The first round of the survey was open from January 30<sup>th</sup> to April 24<sup>th</sup> 2019, with 102 responders (response rate, 72%, females, 40%). Among them, 18% were radiologists, 38% were COPD experts, 38% BE experts, and 7% were pulmonologists working on both diseases. Responders represented 30 countries: Austria, Belgium, Bulgaria, Croatia, Denmark, Estonia, France, Germany, Greece, Ireland, Israel, Italy, Latvia, Lithuania, Macedonia, Malta, Moldova, Netherlands, Norway, Poland, Portugal, Romania, Russia, Serbia, Slovenia, Spain, Sweden, Switzerland, Turkey, UK.

Despite the initial attempt to have a homogenous distribution of survey participants from different European regions, we finally had 7 additional responders from countries with more centres dedicated to COPD and BE in order to ensure the target number of 100 participants. (Figure 1).

After the analysis of results from the 1<sup>st</sup> round, five statements reached positive consensus and passed to the second round: “airways visible within 1cm of the pleura”; “BE in at least one pulmonary segment in more than one lobe”; “lack of tapering sign”; “post bronchodilator FEV1/FVC < 0.7”; “current or past smoking habit ( $\geq 10$  pack-years) or history of other exposure to toxic inhalants (biomass, industrial, etc)” (Figure 2).

Negative consensus was reached only by two statements: 1. “a mixed ventilatory pattern excludes the diagnosis”; 2. “history of positive bronchodilation test excludes the association”.

In the radiology section, three very similar assertions about distribution of BE obtained a high score, although only one reached the consensus threshold. Therefore, the panel decided to include all of them in the second round in order to reiterate the information and achieve a better agreement.

All the other statements obtained an intermediate result, and therefore were excluded from the second round. No microbiological, clinical or pathophysiological items passed the first round, except for history of exposures. To confirm the exclusion of these potentially relevant categories from the definition, the panel introduced new specific questions regarding microbiological and clinical items and gave responders the opportunity to add items with two optional open questions (Table 2).

| <b>TABLE 2. ROUND 2: ADDITIONAL QUESTIONS*.</b>   |  |
|---|--|
| <b>CLINICAL ITEMS REQUIRED TO DEFINE THE ASSOCIATION OF COPD AND BRONCHIECTASIS:</b>        |  |
|   | In addition to the criteria already selected, should any clinical aspect be included in order to ensure only symptomatic patients are considered? (YES/NO)<br><br><i>If answered yes to this question than chose one of the following:</i> |
|   | a) Should the definition of COPD-BE include at least <i>ONE</i> of the following signs and symptoms: cough, expectoration, dyspnoea, fatigue, frequent infections ( $\geq 2$ )?  |
|   | b) Should the definition of COPD-BE include at least <i>TWO</i> of the following signs and symptoms: cough, expectoration, dyspnoea, fatigue, frequent infections ( $\geq 2$ )?  |
|   | c) OPEN QUESTION: is there a sign or symptom you consider essential to define COPD-BE association?   |
| <b>MICROBIOLOGICAL ITEMS REQUIRED TO DEFINE THE ASSOCIATION OF COPD AND BRONCHIECTASIS:</b> |  |
|   | In addition to the criteria already selected, should any microbiological aspect be included? (YES/NO)  |

|  |   |
|--|---|
|  | <i>If answered yes to this question than chose one of the following:</i>  |
|  | a) To define COPD-BE association the following criteria are required: At least one isolation of PPM in sputum in the last year in steady state  |
|  | b) To define COPD-BE association the following criteria are required: >1 isolation of PPM in sputum in the last year  |
|  | c) To define COPD-BE association the following criteria are required: History of chronic bronchial infection (two or more isolates of the same organism at least 3 months apart in 1 year, see ERS guidelines) by any PPM |

*\*Note: in case of an affirmative answer to the primary question, secondary questions (lower case) were performed.*

*Abbreviations: COPD: chronic obstructive pulmonary diseases; BE: bronchiectasis; PPM: potentially pathogenic microorganisms*

b. SECOND ROUND

The second round ran between the end of June and the end of July 2019 and 16 statements were included: 5 on clinical features, 5 on radiological features, 1 on functional features, and 5 on microbiological features (Table 3a). All responders from the first round were contacted and invited to participate once again. The response rate at the second round was 81% (83 responders). As for the first round, radiologists (17/83) were asked to answer exclusively to the radiology section, while respiratory specialists (67/83) completed the entire survey.

Expectedly, all the questions that reached consensus at the first round were confirmed, with a higher level of concordance between responders.

With regards to clinical features, 51 participants (76% of the pulmonologists) agreed on the need to include at least a clinical criterion in the final definition of COPD-BE association. Among them, 84% (43/51) chose to include the presence of at least two symptoms between those listed (cough, expectoration, dyspnoea, fatigue, frequent infections) in the definition. Twenty-nine “yes” responders (56%) also answered the open question: all the proposed symptoms were coherent with those listed in the previous list (Table 3b).

Conversely, the exclusion of microbiological characteristics from the definition was widely confirmed by 61% of pulmonologists (41/67)(Table 3a). Due to the high consensus reached, the panel decided not to perform a third round.

**TABLE 3A: SECOND ROUND RESULTS.** In the second column, the percentage of answers graded 6 point or more. In the third column, the average punctuation received.

| <b>1. Confirmation of statements</b>                             | <b>% of answers</b> | <b>mean score</b> |
|--|---------------------|-------------------|
| Smoking habit and exposures <sup>a</sup>                         | 85%                 | 7,7               |
| Post-bronchodilator FEV1/FVC<0.7 <sup>a</sup>                    | 93%                 | 8.1               |
| Lack of tapering sign <sup>b</sup>                               | 83%                 | 7.3               |
| Airways<1cm of pleura <sup>b</sup>                               | 87%                 | 7.1               |
| BE ≥ 1 pulmonary segment in 1 lobe <sup>b</sup>                  | 64%                 | 5.8               |
| BE > 1 pulmonary segment in 1 lobe <sup>b</sup>                  | 70%                 | 6.2               |
| BE ≥ 1 pulmonary segment in > one lobe <sup>b</sup>              | 73%                 | 6.6               |
| <b>2. Clinical and microbiological aspects<sup>a</sup></b>       |                     |                   |
| <b>2.1 <u>Should any clinical aspect be included?</u></b>        |                     |                   |
|  | <b>YES</b>          | <b>76%</b>        |
| <b>Between “yes” responders (n. 51)</b>                          | <b>% of answers</b> | <b>mean score</b> |
| At least ONE symptom   | 65%                 | 5.9               |
| At least TWO symptoms  | 84%                 | 7.5               |
| <b>2.2 <u>Should any microbiological aspect be included?</u></b> |                     |                   |
|  | <b>YES</b>          | <b>39%</b>        |
| <b>Between “yes” responders (n. 26):</b>                         | <b>% of answers</b> | <b>mean score</b> |
| At least one isolation of PPM stability                          | 65%                 | 6.1               |
| >1 isolation of PPM in sputum in the last year                   | 54%                 | 5.7               |
| Chronic bronchial infection by any PPM                           | 65%                 | 6.4               |
| <i>Pseudomonas</i> ever isolated in sputum                       | 46%                 | 5.2               |

Where not specified, expressed percentages refer to the number of responders: a) 67 responders (only pulmonologists); b) 83 responders (pulmonologists + radiologists).

*Abbreviations.* FEV1: Forced Expiratory Volume in the 1st second; FVC: Forced Vital Capacity; BE: Bronchiectasis; PPM: Potential Pathogenic Microorganisms.

| Table 3b: answers to open question “is there a sign or symptom you consider essential to define BE-COPD association”. |               |   |
|---|---------------|---|
| Open question:  | N° of answers |   |
| <b>Total responders:</b>  | 29            |   |
| - <b>Expectoration</b>  | 18            | bronchorrhoea, chronic sputum, chronic phlegm, phlegm production, purulent sputum   |
| - <b>Cough</b>  | 4             |   |
| - <b>Recurrent infections</b>   | 11            | frequent infections, frequent lower respiratory infections, more than 1 exacerbation/year, infections including pneumonia |

Answers were grouped into three clusters according to similarity of answers. Detailed answers are listed in third column.

According to final responses of the second round, the panel formulated the consensus definition expressed in Table 4.

| Table 4. Final consensus definition.   |   |
|--|---|
| <b>The association of COPD and BE is defined as the presence of at least 4 elements:</b> |   |
| 1.   | <b>RADIOLOGICAL: Abnormal bronchial dilatation in one or more pulmonary segment in more than one lobe and specific radiological findings (airways visible within 1cm of pleura and/or lack of tapering sign) plus</b> |
| 2.   | <b>OBSTRUCTION: a functional obstructive pattern (post-bronchodilator FEV1/FVC&lt;0.7), plus</b>  |
| 3.   | <b>SYMPTOMS: 2 or more of the following symptoms: cough, expectoration, dyspnoea, fatigue, frequent lower airway infections(≥2/year) plus</b>   |
| 4.   | <b>EXPOSURE: current or past smoking habit (≥10pack-years) or other toxic exposure (biomass, industrial etc.)</b>   |

These criteria form the “ROSE” acronym (Radiology, Obstruction, Symptoms, Exposure, figure 3).

## DISCUSSION

The need to phenotype chronic respiratory disease patients has been frequently raised, mostly in order to adopt personalized treatments and improve outcomes[30–32]. This is particularly

challenging when different pathological conditions co-exist, as in the case of COPD-BE association.

The presence of COPD and BE in a single patient has frequently been reported[4–6, 16]. Furthermore, numerous studies have shown that this association has a more severe clinical presentation and worse prognosis than each individual disease[16, 17, 33–38]. However, there is no consensus on how this association should be defined. Indeed, many experts have provided different interpretations of this association[4, 39]. Some authors such as Hurst et al. have discussed the existence of a ‘COPD-BE overlap syndrome’[4, 40] which might suggest the existence of a unique and distinctive clinical entity with different clinical, radiological or biological characteristics compared to the two diseases alone[4]. However, after internal discussion, the panel decided not to adopt an overlap definition for coexisting COPD and BE, considering the lack of supporting evidence. At the present time, the understanding of biological and pathogenetic interaction between these two conditions is still poor and, in our opinion, definitely not enough to justify the description of a new clinical entity. Alternative concepts have been proposed, including the idea of using clinical criteria to determine the “dominant” condition for therapy, either BE as a phenotype of COPD or chronic airflow obstruction in a patient with BE. This approach is difficult to standardise across different centres as objective methods of defining dominant conditions have not yet been defined. Instead, the panel decided to consider the presence of COPD and BE as an association of two different defined diseases, with complex and not fully understood mutual interactions.

The pathophysiology of this association is still uncertain. Indeed, it is not clear whether the presence of BE could increase susceptibility to tobacco smoking, leading to more rapidly progressive functional and clinical decline and, therefore, the development of COPD; or conversely, whether the development of BE could be part of the natural history of COPD[4]. Recently, a long term observational study by Martinez-Garcia et al. identified the presence of chronic purulent sputum production, potentially pathogenic microorganisms (PPM) in sputum and frequency of hospitalizations due to COPD exacerbations as independent, preventable and treatable risk factors for BE emergence or progression in COPD patients[25]. More data are needed to unravel this issue and we believe that a definition is crucial in order to optimise the development of evidence in the field, to guide future trials and to produce useful clinical recommendations.

To satisfy these needs, the definition should be simple, clear and helpful, and ideally useful for clinical settings as well as for research. Due to the lack of agreement in the current literature,

we decided to approach this problem by assessing the opinion of professionals with different backgrounds, through a Delphi survey, and, finally, to produce a consensus definition. To our knowledge, this is the first attempt to systematically address this need.

An optimal geographical distribution of responders was sought, but unfortunately it could be only partially achieved. In fact, Eastern Europe, the most populated European region, only accounted for 16% of respondents, while most came from the UK, Spain and other central and southern European countries. It possibly reflects the different levels of experience and scientific interest in BE across European countries, also suggested by preliminary data from the European BE registry (EMBARC) [41]. Of course, this distribution is a potential source of bias, due to the variability between different geographical areas in terms of BE aetiologies, prevalence of COPD, smokers, tuberculosis, etc.

The final consensus definition of the association COPD and BE corresponds to the acronym ROSE for the four components: Radiology, Obstruction, Symptoms and Exposure. Responses obtained from participants reflect the importance of radiology for the diagnosis of BE in COPD patients. In fact, highest consensus was obtained by statements derived from Naidich criteria[42]; however, statements regarding the extent and distribution of BE had to be reiterated on the second round for confirmation, when finally a clear agreement was achieved: abnormal bronchial dilatation needs to be extensive (“one or more pulmonary segment in more than one lobe”) to define the pathological association of COPD and BE.

Other radiological criteria such as the presence of bronchial wall thickening received a borderline score (68%). Both radiologists and pulmonologists in the panel agreed on excluding it from the second round, being a non-specific marker of inflammation present in different respiratory conditions. Similarly, the broncho-arterial (BA) ratio was not included in the statements of our survey, due to its lack of specificity for the association COPD-BE. As stated before, the BA ratio in patients with both COPD and BE can be influenced by several factors, such as, pulmonary hypoxic vasoconstriction, advanced age, increased vessel size due to pulmonary hypertension, among others[18, 43].

According to GOLD, bronchial obstruction is needed to define the presence of COPD[3], therefore, representing an essential feature in any comorbid association. Indeed, the presence of airflow obstruction is a necessary but not sufficient condition to establish a COPD diagnosis. Conversely, in pure BE a wide variability of functional patterns has been described[22]. Persistent airflow obstruction is frequent in symptomatic BE patients without smoking history or other risk factors for COPD. This could be associated with misdiagnosed COPD in a variable

proportion of BE patients, possibly leading to a delay in BE diagnosis if HRCT is not performed [22, 44–46].

Regarding symptoms, no clinical criteria reached the expected level of consensus in the first round. Nevertheless, considering the importance of clinical manifestations in both COPD and BE, the panellists considered the possibility that the first-round statements might have lacked clarity and reformulated them in the second round, getting the approval of most responders. Indeed, the included symptoms are unspecific and common to a variety of chronic respiratory conditions, but still necessary to define this clinical association. The panel used the following threshold to define 'frequent lower airway': at least two exacerbations/year or one hospitalization/year. This decision was taken in consideration of the available literature on frequent exacerbator phenotypes in both COPD and BE[47–51]. The inclusion of smoking or toxic exposures received a high level of consensus since the first round. In fact, cigarette smoking represent the main risk factor for COPD in high-income countries [3]. The threshold of 10 pack-years was chosen since it is generally accepted as the minimum significant exposure to develop COPD [3]. Biomass exposure was also considered for the definition as it can be a relevant cause of COPD in low-income countries[53], and COPD development can be expected after 10-15 years of exposure[54, 55].

Apart from the criteria that were included in the ROSE definition, we explored other aspects of the association COPD-BE which did not reached consensus. For instance, none of the statements proposed in the pathophysiological section achieved consensus, highlighting the fact that we currently lack any relevant biological marker of this association. Among the excluded variables, age >35 years (68%) obtained a borderline score. In concordance with the responders, although the association of COPD-BE is a disease of the adult population, the panellists also felt that it was impossible to define an age threshold for the onset of both COPD and BE. This decision finds confirmation in a prevalence study from China where increasing number of individuals with COPD were aged right above 20 years[56].

Despite the importance of respiratory infections, respondents did not consider microbiological criteria essential to define the COPD-BE association. Respiratory infections are one of the most frequent clinical manifestations and alarm signs to suspect bronchiectasis, while in COPD they are a potential marker of disease severity and/or can suggest the need for a therapeutic step-up. Nevertheless, respiratory infections do not represent an exclusive criterion to define any respiratory condition, being non-specific complications of most airways' diseases.

However, in view of ongoing research on clinical and biological phenotypes of the COPD-BE association, the perceived importance of biological or microbiological markers could change in the future. For example, isolation of *Pseudomonas aeruginosa* or *Haemophilus influenzae* has been already identified as a risk factor for BE in patients with COPD[24, 57, 58]. Moreover, both bacterial or fungal airways infections have been described as being more prevalent in patients with both COPD and BE [59–61] though no specific phenotypes have been identified yet.

In conclusion, the EMBARC Working Group on Airways diseases agreed that the definition of COPD-BE association requires the coexistence of specific radiological signs and a functional obstructive pattern associated to the presence of at least two characteristic symptoms and current or past exposure to smoke or other toxic agents, which can be summarised in the acronym ROSE.

Future validation of this definition in a clinical setting is necessary, together with pheno- and/or endotyping studies to assess the biological and functional patterns of patients with COPD and BE. In this group of patients, the identification of treatable traits will be important for management, appropriate enrolment in clinical trials and for new drug registration purposes.

Hopefully, the present consensus definition of COPD-BE can be the first step [in guiding risk stratification and clinical management of patients with this association after an appropriate validation in international cohorts of patients with COPD and/or BE.](#)

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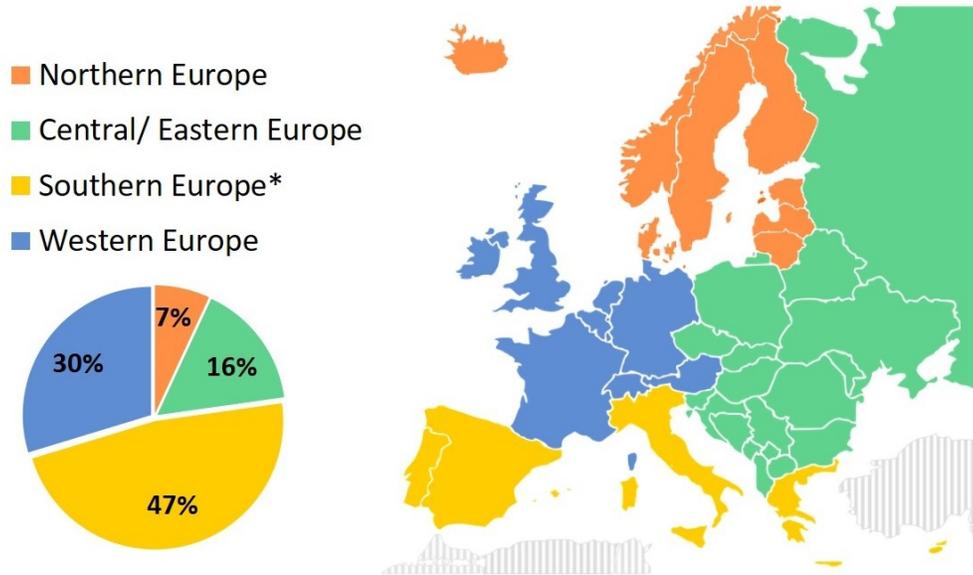


Figure 1. Geographical distribution of participants to the survey. Countries have been grouped according to EuroVoc criteria.[23] \*Only European countries are represented in the map; responders from Turkey and Israel have been included in the "Southern Europe" region.

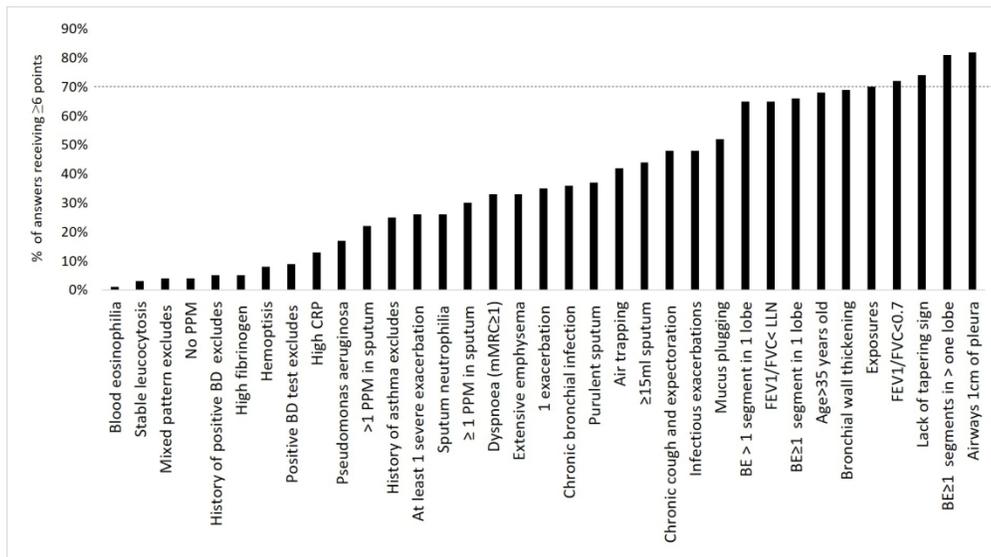


Figure 2. Results from the first round. Statements were graded from 1 (completely disagree) to 9 (completely agree). Consensus was defined as at least 70% of answers scored 6 or higher (dashed line). Abbreviations. PPM: Potential Pathogenic Microorganisms; BD: bronchodilation test; CRP: C-Reactive Protein; mMRC: modified Medical Research Council; BE: Bronchiectasis; FEV1: Forced Expiratory Volume in the 1st second; FVC: Forced Vital Capacity; LLN: Lower Limit of Normal.

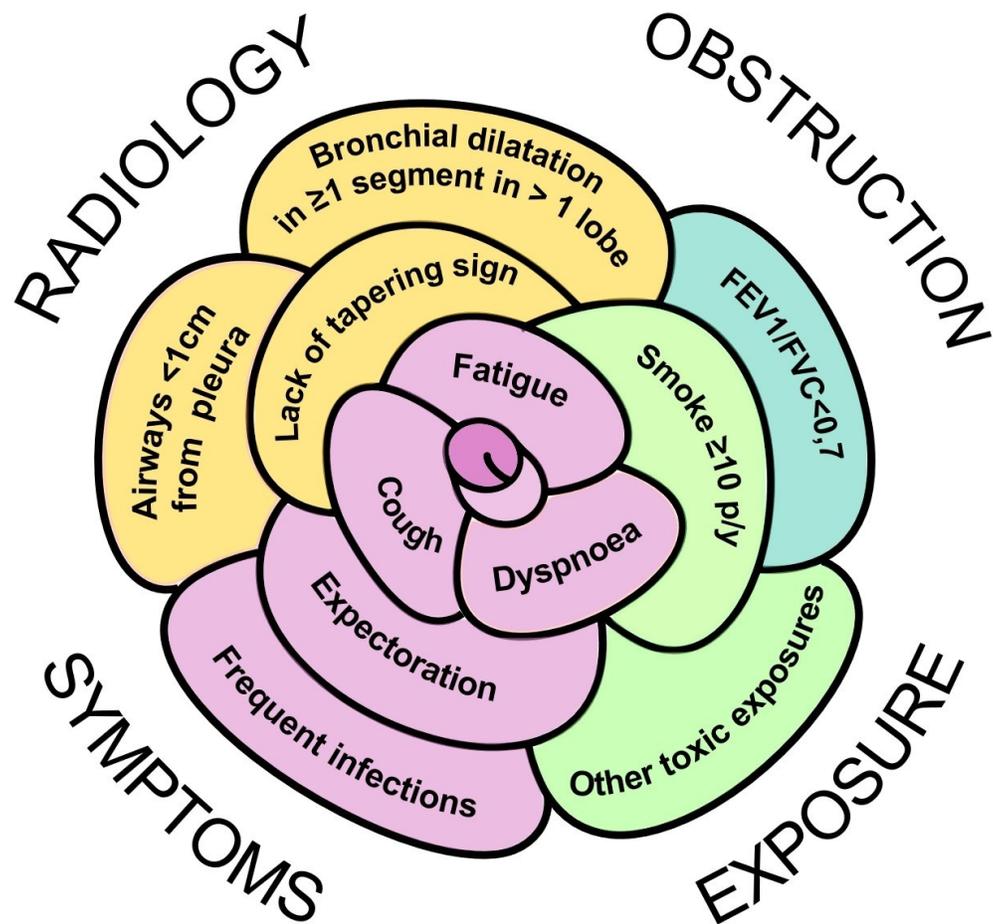


Figure 3 The "ROSE" criteria: Radiology, Obstruction, Symptoms, Exposure, defining the association of COPD and Bronchiectasis. FEV1: Forced Expiratory Volume in the 1st second; FVC: Forced Vital Capacity; p/y: pack-years.