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PHENOTYPING AIRWAYS DISEASES IN BRONCHIECTASIS: THE ABCS PROTOCOL (ASTHMA – BRONCHIECTASIS – COPD – CHRONIC RHINO-SINUSITIS)

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PhD THESIS

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LIST OF ABBREVIATIONS AND ACRONYMS

AAT	Alpha-1 Antitrypsin
ABPA	Allergic Bronchopulmonary Aspergillosis
ACT	Asthma Control Test
AERD	Aspirin-Exacerbated Respiratory Disease
AFRS	Allergic Fungal Rhinosinusitis
ATB	Antibiotics
ATS	American Thoracic Society
AUC	Area Under the Curve
AWD	Airways Disease
AWG	Airway Working Group
BA	Bronchoarterial ratio
BD	Bronchodilator
BMI	Body Mass Index
BPG	Best Practice Guideline
BSI	Bronchiectasis Severity Index
BWT	Bronchial Wall Thickening
CAT	COPD Assessment Test
CBC	Complete Blood Count
CBI	Chronic Bacterial Infection
CCAD	Central Compartment Atopic Disease
CF	Cystic Fibrosis
CRF	Case Report Form
CRP	C-Reactive Protein
CT	Computed Tomography
DLCO	Diffusing Capacity of the Lung for Carbon Monoxide
ELTGOL	Expiration Lente Totale Glotte Ouverte en décubitus Latéral (French drainage technique)
ENT	Ear, Nose and Throat
EPOS	European Position Paper on Rhinosinusitis and Nasal Polyps
ER	Emergency Room
ERS	European Respiratory Society

FACED	Score based on FEV1, Age, Chronic colonization, Extension, Dyspnea
FENO	Fractional Exhaled Nitric Oxide
FEV	Forced Expiratory Volume
FEV1	Forced Expiratory Volume in 1 second
FU	Follow-Up
FVC	Forced Vital Capacity
GEMA	Spanish guideideline for the diagnosis and management of asthma
GERD	Gastroesophageal Reflux Disease
GGO	Ground-Glass Opacity
GINA	Global Initiative for Asthma
GPA	Granulomatosis with Polyangiitis
HRCT	High-Resolution Computed Tomography
HVH	Hospital Vall d'Hebron
ICS	Inhaled Corticosteroids
IFN-γ	Gamma Interferon
IL	Interleukin
ILC2	Type 2 Innate Lymphoid Cells
IQR	Interquartile Range
KMBARC	Korean Multicenter Bronchiectasis Audit and Research Collaboration
LABA	Long-Acting Beta-Agonist
LAMA	Long-Acting Muscarinic Antagonist
LFT	Lung Function Test
LQR	Lower Quartile Range
LTRA	Leukotriene Receptor Antagonist
M2	M2 Macrophage phenotype
MP	Mucus Plugging
NA	Not Applicable
NE	Neutrophil Elastase
NET	Neutrophil Extracellular Trap
NSDA	Non-Steroid Dependent Asthma
NTM	Nontuberculous Mycobacteria

O2	Oxygen
OCS	Oral Corticosteroids
PA	Pseudomonas aeruginosa
PBD	Post-Bronchodilator
PCD	Primary Ciliary Dyskinesia
PEF	Peak Expiratory Flow
PPM	Potentially Pathogenic Microorganism
ROC	Receiver Operating Characteristic
ROS	Reactive Oxygen Species
SABA	Short-Acting Beta-Agonist
SAMA	Short-Acting Muscarinic Antagonist
SD	Standard Deviation
SDA	Steroid Dependent Asthma
SLPI	Secretory Leukocyte Protease Inhibitor
SUA	Severe Uncontrolled Asthma
T1	Type 1 immune response
T2	Type 2 immune response
T3	Type 3 immune response
TGF	Transforming Growth Factor
TLC	Total Lung Capacity
TNF	Tumor Necrosis Factor
UAS	Upper Airway Symptoms
UK	United Kingdom
USA	United States of America

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RESUMEN

Introducción:

Las bronquiectasias (BQ) representan una enfermedad respiratoria crónica caracterizada por la presencia de dilataciones bronquiales permanentes y sintomas característicos cuales tos y expectoración e infecciones recurrentes. Debido a que las bronquiectasias pueden ser el resultado de condiciones muy distintas, esta enfermedad presenta una gran variabilidad y heterogeneidad en la presentación clínica, el grado de afectación y el pronóstico. En algunos pacientes, las BQ pueden asociarse a otras enfermedades de la vía aérea, especialmente asma, enfermedad pulmonar obstructiva crónica (EPOC) y rinosinusitis crónica (RSC). La prevalencia y el impacto de la presencia de comorbilidades de la vía aérea en pacientes con BQ han sido investigados por varios autores en los últimos años. Sin embargo, la falta de homogeneidad en la definición de estas patologías, la superposición de síntomas entre distintas entidades y la ausencia de pruebas diagnósticas específicas dificultan la comparabilidad y reducen la precisión de dichos estudios. Nuestro estudio se centró en la caracterización de la vía aérea en pacientes con BQ, con el fin de identificar perfiles clínicos diferenciados y potenciales marcadores diagnósticos de comorbilidades respiratorias asociadas.

Métodos:

En nuestro estudio se reclutaron pacientes con BQ sin comorbilidades respiratorias diagnosticadas previamente, quienes fueron sometidos a una evaluación exhaustiva de sus características clínicas. Esta incluyó valoración de síntomas, pruebas completas de función respiratoria, análisis de biomarcadores inflamatorios, estudio radiológico (incluyendo hallazgos no habitualmente asociados a BQ), caracterización microbiológica y cuestionarios de calidad de vida específicos para cada una de las enfermedades respiratorias. Se aplicaron criterios diagnósticos clínicos, funcionales y biológicos para identificar la presencia de asma, EPOC y RSC asociadas.

Resultados:

Se incluyeron 77 pacientes con BQ, predominantemente mujeres (79.2%), con una edad media de 58.1 años. La mayoría refirió tos y expectoración, con impacto moderado en los cuestionarios de calidad de vida (SGRQ y LCQ). Sorprendentemente, más del 60% de los pacientes refirió haber presentado sibilancias. Los síntomas de vías aéreas superiores estuvieron presentes en el 40% de los casos.

El 43.1% tenía infección bronquial crónica, siendo *Pseudomonas aeruginosa* el patógeno más frecuente. El 85.7% de los pacientes recibía tratamiento respiratorio crónico, con un

uso elevado de macrólidos (41.6%) e inhaladores (72.7%). Solo el 40.3% seguía tratamiento fisioterápico de forma regular.

Desde un punto de vista funcional, un 27.6% mostró un patrón obstructivo y un 11.3% un patrón restrictivo. En el 37% se evidenció atrapamiento aéreo. Solo el 5.2% presentó una respuesta broncodilatadora significativa. Solo el 20% de los pacientes presentó valores de función pulmonar completamente normales.

El 25.7% mostró niveles elevados de FeNO. El 15.6% de los pacientes presentó eosinofilia en sangre periférica, la cual se asoció con menor purulencia del esputo y menor prevalencia de infección crónica por *PA*.

Para investigar la presencia y expresión fenotípica de comorbilidades respiratorias se analizó el conjunto de variables clínico-instrumentales y se realizaron los cuestionarios más comunes de cada una de las enfermedades: CAT, ACT, SGRQ y SNOT-22.

Los cuestionarios se asociaron de manera variable con algunas características clínicas. El SGRQ mostró correlación con el FEV_1 (en litros) y la disnea, al igual que el CAT, que también se correlacionó con la frecuencia de exacerbaciones. En cambio, el ACT y el SNOT no mostraron correlación con ninguna variable clínica. No obstante, los cuatro cuestionarios presentaron correlación significativa entre sí.

Con respecto a la asociación BQ-asma, se observó que el 46.8% de los pacientes presentaba síntomas compatibles con el criterio clínico mayor de asma, pero solo el 5.2% cumplió criterios diagnósticos completos al considerar pruebas funcionales y biomarcadores inflamatorios. Un 26% fue clasificado como "sospecha de asma", mientras que en el 68.8% de los casos se descartó el diagnóstico por no cumplir criterios suficientes. Los pacientes con asma confirmada o sospechada presentaron características similares a aquellos en los que el diagnóstico fue descartado, aunque se observó un índice de masa corporal más elevado, una tendencia a mayor extensión radiológica de las BQ y un uso más frecuente de corticoides inhalados.

La evaluación de la comorbilidad BQ-EPOC se realizó aplicando los criterios ROSE. BQ-EPOC se identificó en el 9.1% de los pacientes a pesar de que inicialmente no tuviesen diagnóstico de EPOC asociado. Estos presentaron valores más bajos de FEV1/FVC, sin diferencias clínicas relevantes respecto a los subjetos sin coexistencia de EPOC.

Con respecto a CRS, esta se diagnosticó en el 31.5% de la cohorte. Los síntomas predominantes fueron obstrucción nasal y congestión, con confirmación instrumental (TC de senos y/o endoscopia) en un tercio de los casos. Los pacientes con RSC presentaron

puntuaciones significativamente peores en el escore SNOT-22, mayor producción de expectorado y menor extensión radiológica de la BQ, aunque no se observaron diferencias en función pulmonar ni en la frequencia de exacerbaciones.

Conclusión:

Las comorbilidades respiratorias son altamente prevalentes en pacientes con BQ, pero su diagnóstico sigue siendo complejo, especialmente en el caso del asma, debido a la inespecificidad de los síntomas. Este estudio resalta la necesidad de establecer criterios diagnósticos objetivos y desarrollar herramientas clínicas prácticas para la detección de asma y RSC en BQ. La sola presentación clínica no parece suficiente para identificar a los pacientes con mayor probabilidad de presentar asma o RSC y los cuestionarios específicos por enfermedad tampoco parecen aportar valor en la identificación de posibles fenotipos por su escasa correlación con los parámetros clínicos y funcionales. En particular, la realización sistemática de pruebas de provocación bronquial podría ayudar a clarificar la verdadera prevalencia del asma en esta población. Estudios adicionales en cohortes más amplias serán fundamentales para validar estos hallazgos.

ABSTRACT

Introduction:

Bronchiectasis (BE) is a chronic respiratory disease characterized by permanent bronchial dilatation and typical symptoms such as cough, sputum production, and recurrent infections. Since bronchiectasis can result from a wide range of conditions, it exhibits great variability and heterogeneity in clinical presentation, severity, and prognosis. In some patients, BQ may be associated with other airway diseases, particularly asthma, chronic obstructive pulmonary disease (COPD), and chronic rhinosinusitis (CRS). The prevalence and impact of these airway comorbidities in patients with BE have been investigated by several authors in recent years. However, the lack of consistent definitions, overlapping symptoms between conditions, and the absence of specific diagnostic tests complicate comparability and reduce the accuracy of these studies. Our study focused on the characterization of the airway in patients with BE, aiming to identify distinct clinical profiles and potential diagnostic markers of associated respiratory comorbidities.

Methods:

We recruited patients with BE without a previous diagnosis of respiratory comorbidities, who underwent a comprehensive clinical assessment. This included symptom evaluation, full pulmonary function testing, analysis of inflammatory biomarkers, radiological studies (including findings not usually associated with BE), microbiological characterization, and disease-specific quality-of-life questionnaires for each respiratory condition. Clinical, functional, and biological diagnostic criteria were applied to identify the presence of associated asthma, COPD, and CRS.

Results:

A total of 77 BE patients were included, predominantly female (79.2%), with a mean age of 58.1 years. Most reported cough and sputum production, with moderate impact on quality-of-life questionnaires (SGRQ and LCQ). Surprisingly, more than 60% reported having experienced wheezing. Upper airway symptoms were present in 40% of cases.

Chronic bronchial infection was found in 43.1%, with *Pseudomonas aeruginosa* being the most frequent pathogen. A total of 85.7% were on chronic respiratory treatment, with high usage of macrolides (41.6%) and inhalers (72.7%). Only 40.3% regularly followed a physiotherapy regimen.

From a functional perspective, 27.6% showed an obstructive pattern and 11.3% a restrictive pattern. Air trapping was observed in 37%, while only 5.2% had a significant bronchodilator response. Only 20% had completely normal pulmonary function values.

Elevated FeNO levels were found in 25.7%. Peripheral blood eosinophilia was present in 15.6% of patients and was associated with lower sputum purulence and lower prevalence of chronic *Pseudomonas aeruginosa* infection.

To explore the presence and phenotypic expression of respiratory comorbidities, we analyzed clinical-instrumental variables and administered the most common questionnaires for each disease: CAT, ACT, SGRQ, and SNOT-22.

The questionnaires showed variable associations with clinical characteristics. The SGRQ correlated with FEV1 (in liters) and dyspnea, as did the CAT, which also correlated with exacerbation frequency. In contrast, ACT and SNOT showed no correlation with any clinical variable. However, all four questionnaires showed significant correlation with each other.

Regarding the BE-asthma association, 46.8% of patients had symptoms consistent with the major clinical criterion for asthma, but only 5.2% met full diagnostic criteria when functional tests and inflammatory biomarkers were included. A total of 26% were classified as “suspected asthma,” while in 68.8% of cases, the diagnosis was ruled out due to insufficient criteria. Patients with confirmed or suspected asthma showed similar characteristics to those in whom the diagnosis was excluded, although they had a higher body mass index, a trend toward greater radiological extent of BE, and more frequent use of inhaled corticosteroids.

The evaluation of BE-COPD comorbidity was based on the ROSE criteria. BE-COPD was identified in 9.1% of patients, despite the absence of a prior COPD diagnosis. These patients showed lower FEV_1/FVC values, with no significant clinical differences from the rest of the group.

As for CRS, it was diagnosed in 31.5% of the cohort. The predominant symptoms were nasal obstruction and congestion, with instrumental confirmation (sinus CT and/or endoscopy) in one-third of cases. Patients with CRS had significantly worse SNOT-22 scores, higher volumes of sputum production, lesser radiological BE extension, although no differences were observed in pulmonary function or exacerbation frequency.

Conclusions:

Respiratory comorbidities are highly prevalent in patients with BE but their diagnosis remains challenging, especially in the case of asthma, due to the nonspecific nature of

symptoms. This study highlights the need to establish objective diagnostic criteria and to develop practical clinical tools for detecting asthma and CRS in BE. Clinical presentation alone does not seem sufficient to identify patients with a higher likelihood of having asthma or CRS, and the disease-specific questionnaires also do not seem to add value in identifying possible phenotypes due to their low correlation with clinical and functional parameters. In particular, systematic bronchial provocation testing could help clarify the true prevalence of asthma in this population. Further studies in larger cohorts will be essential to validate these findings.

1. INTRODUCTION

1.1 AIRWAYS DISEASES AT A GLANCE

Under the definition of chronic airways diseases (AWDs) are included a variety of different pathological conditions that affect both upper and lower airways, being COPD, asthma, BE and CRS the most common. Globally, these diseases represent the most common chronic respiratory diseases: according to a 2019 report, COPD and asthma alone are responsible of more than 2/3 of all reported cases of chronic respiratory diseases, and are the cause of most of the related deaths (1).

AWDs have been well known since very early in human history: the first reference to asthma in occidental culture dates back to the 4th century B.C, mentioned by the Corpus Hippocraticum initiated by Hippocrates, where the term ἅσμα (read: *asma*), literally meaning "panting", was firstly used to describe the presence of dyspnea (2).

However, the disease made his appearance in far older document from other parts of the world: descriptions of symptoms compatible with asthma appear in the most antique medicine textbook of witch we have knowledge, the Chinese "Nei Ching"(3). This text, dating back to a period between the 4th and 2nd centuries BC, gathers medical, philosophical, and religious knowledge that is believed to have originated as far back as the 26th century BC(4). Also, remedies for rhinosinusitis and asthma are described in the Ebers Papyrus, a compendium of Egyptian medical knowledge and tradition that dates back to the 1500 BC(4).

On the other hand, the first descriptions of COPD, particularly regarding emphysema as observed in anatomical pathology, is much more recent. Initial references to "voluminous lungs" date back to the late 17th century, while Laennec, in 1821, described abnormally inflated lungs accompanied by abundant mucus in the airways, consistent with what we now recognize as chronic bronchitis with emphysema (5,6). However, it was not until the second half of the 20th century that the term "chronic obstructive pulmonary disease" began to appear, as well as its established association with cigarette smoking (6–8).

To Laennec we also owe the first description of bronchiectasis in 1819, defined as the abnormal dilatation of bronchi and bronchioles following repeated cycles of infections(9), while William Osler in late 1800 contributed to the clinical understanding of bronchiectasis by recognizing its association with recurrent chest infections, mucus hypersecretion, and haemoptysis. Ironically, he died of a pulmonary empyema, likely resulting from complicated pneumonia secondary to undiagnosed localized bronchiectasis, as revealed by his autopsy(10).Indeed, while signs and symptoms of respiratory diseases have been reported since ancient times, formal description and categorisation of each clinical entity, as well as

the correlation between symptoms and underlying physiopathological mechanisms, has been possible only starting from the 19th century, thanks to medical progress and technological advances (11).

The description of lung function, starting with the invention of the first modern spirometer by Hutchinson in 1846 and perfectioned starting from the 1920s, opened a completely new scenario for pulmonologists(12). The introduction of chest radiography, shortly after the discovery of X-rays from Roentgen in 1895, represented a further revolution, allowing physicians to *look inside* alive patients and correlate clinical presentation and imaging. With the advent of computed tomography in 1972, pulmonology was changed beyond recognition(11,13).

These advances progressively enhanced the understanding of respiratory diseases, paving the way for more accurate classifications and the development of increasingly effective and individualized therapeutic approaches.

In the last few decades, the shift towards precision medicine has expanded the concept of diseases, transforming them from single entities primarily defined by key symptoms and progression into a spectrum of diverse clinical presentations (phenotypes) and underlying pathological pathways (endotypes).

However, AWDs are characterised by a wide range of symptoms and signs, often overlapping and escaping traditional disease definition.

1.1.1 ASTHMA

Asthma represents a common chronic disease, with a prevalence rate in the general population varying between 1-29% depending on the country. It can affect any age group, and it is the most frequent chronic disease in the paediatric population(14).

It is characterized by the presence of typical symptoms such as cough, wheezing, dyspnea, and chest tightness. These symptoms can vary over time and usually occur in response to stimuli such as exposure to allergens or irritants, viral infections, physical exercise, temperature or humidity changes, and environmental pollution(15,16). Typically, phases of stability and symptom absence alternate with phases of exacerbation of variable frequency and intensity. Functionally, this is reflected in airflow obstruction, which can also be variable and identifiable during acute phases or even in stable state (14).

From a pathophysiological perspective, it is impossible to speak of a single mechanism responsible for the development of the disease. Different cellular and molecular pathways

endotypes have been described, which translate clinically into a range of phenotypes and may represent different therapeutic targets(17).

The two fundamental endotypes are called Th2-high or endotype 2, and Th2-low, according to the predominant CD4+ T lymphocyte population involved in the process.

The pathophysiology of Th2-mediated asthma (or endotype 2) is complex, involving both innate and adaptive immunity(18).

The presence of dysregulation at the level of the respiratory epithelial barrier allows the penetration of external elements such as allergens, pollutants, and viruses. In response, the production of a class of substances called “epithelial alarmins” is activated, contributing to the inflammatory cascade in various ways.

On one hand, they induce dendritic cells and naive CD4+ T helper cells to differentiate into Th2 cells, amplifying the inflammatory cascade through cytokines (including interleukine(IL)-4, IL-5, IL-9, and IL-13)(19).

IL-4 stimulates B lymphocytes to produce IgE, which bind to basophils and mast cells. These, in turn, attract eosinophils and release other mediators such as serotonin, histamine, and tryptase(18). IL-5 also contributes to eosinophilia as it promotes the differentiation of eosinophils in the bone marrow. All these mechanisms finally collaborate in the activation of bronchial smooth muscle, resulting in bronchial hyperreactivity, smooth muscle hypertrophy, and airway remodelling through the activation of fibroblasts(17).

Additionally, there is an increase in mucus production due to the increased expression of goblet cells driven by IL-4 and IL-13(20).

Advances in understanding Type 2 (T2)/Th2-high asthma have been crucial for the development of drugs that target one or more key pathogenic pathways.

In contrast, the mechanisms responsible for Th2-low inflammation remain poorly understood. Among the most studied mechanisms, increased activation of Th1 cells and the presence of an imbalance at the level of Th17/Treg cells have been described(17). In patients with Th1-mediated asthma, increased levels of gamma interferon (IFN-**γ**) are associated with increased airway resistance and inflammatory infiltrates. IFN-**γ** would reduce the expression of the secretory leukocyte protease inhibitor (SLPI), an antiprotease with a protective effect at the mucosal level, whose reduction causes bronchial hyperreactivity that is refractory to corticosteroid treatment(21).

On the other hand, Th17 activation leads to an increase in the production of IL-17, which promotes neutrophilic inflammation and airway remodeling through the proliferation of smooth muscle cells and fibroblasts(22).

In general, what characterizes Th2-low asthma patients is the reduced or absent response to corticosteroids and the neutrophilic or paucigranulocytic profile, i.e., greater than 40-60% neutrophils or a normal distribution of neutrophils and eosinophils in sputum(17).

These two endotypes correspond to a variety of phenotypes, which have been classified in different ways over time, without standardized definitions. The proposed classifications focus on one or more aspects, including the age of onset (early or late), triggering factors (allergic, occupational, aspirin-induced, exercise-induced, smoking-associated asthma), the predominant cellularity type (eosinophilic, neutrophilic, paucigranulocytic), functional characteristics (with chronic fixed obstruction), the response to corticosteroid treatment, and other clinical characteristics of the patients (associated with obesity, menstruation, comorbidities, etc.)(18,23,24).

Correct phenotypic identification is more relevant in the case of severe uncontrolled asthma (SUA): the Spanish guideline for the diagnosis and management of asthma (GEMA) proposes three phenotypes in this case: allergic, eosinophilic, and non-T2(25).

Allergic asthma (T2) is characterized by the described T2 inflammatory pattern, eosinophilic or mixed cellularity in sputum, and symptom onset after exposure to allergens. Eosinophilic asthma (T2) presents with clearly eosinophilic inflammation, demonstrable in the bronchial mucosa and sputum, regardless of the presence of atopy and despite treatment with high doses of corticosteroids. It often presents with chronic rhinosinusitis and polyposis and can be triggered by pharmacological stimuli (aspirin). Non-T2 asthma presents without eosinophilia in both peripheral blood and sputum, low FeNO levels, poor response to corticosteroids, frequent chronic airflow limitation, and/or smoking(25).

Depending on the disease severity, chronic or as-needed medical treatments may be necessary to control symptoms.

Among chronic treatments, classified as “control” or maintenance treatments, are inhaled corticosteroids (ICS) or systemic glucocorticoids, leukotriene receptor antagonists (LTRA), long-acting beta2 agonists (LABA), and anticholinergics (tiotropium)(25). In the last two decades, biologic treatments have been added, which will be discussed later in this chapter.

Relieve treatments are used to rapidly treat bronchoconstriction or prevent it in the case of known triggers (e.g., physical exercise). These include short-acting beta2 agonists (SABA)

and short-acting inhaled anticholinergics (SAMA), as well as some ICS/LABA combinations such as budesonide/formoterol, beclometasone/formoterol, and beclometasone/salbutamol(25) .

1.1.2 BRONCHIECTASIS

The term "bronchiectasis" primarily refers to a radiological finding: the abnormal dilation of the bronchi, due to various mechanisms of airway remodeling. In some patients, it may be secondary to traction, resulting in asymptomatic dilations with no clinical significance. Bronchial dilatation is usually defined by the presence of an inner or outer airway–artery diameter ratio ((PCDrial ratio, BA) of 1,5 or more, lack of tapering of the airways, and airways visible in the periphery(26). In contrast, when we talk about bronchiectatic disease, we refer to a syndrome characterized by the presence of this radiological finding associated with characteristic symptoms, particularly hyperproduction of secretions and recurrent infections(27).

It is a heterogeneous disease in both its clinical manifestations and its causes, whether respiratory or systemic, although there are common pathogenic elements.

Regardless of the aetiology, the airways of patients with BE exhibit alterations in local or systemic defences, which increase susceptibility to infections and their chronicity. Inflammation caused by infections leads to airway remodelling, mucus hyperproduction, and the impairment of mucociliary clearance (intrinsic in some aetiologies, or secondary to inflammation and bronchial dilation), making it more difficult to manage secretions and perpetuate the vicious cycle of Cole(28,29). The pathological process can originate from any of these four elements: infection, inflammation, structural deformation, and impairment of secretion clearance, all of which interact synergistically, meaning that treating one element does not necessarily stop the pathological process.

Thus, the "vicious vortex" model is currently used to describe the complex interactions between all the elements involved in the development and evolution of BE(28).

The aetiological diagnosis is a key point in managing patients with BE, as some causes have specific treatments or require specific management. When the etiological investigation does not identify a cause, the condition is defined as "idiopathic"(30).

The prevalence of different aetiologies largely depends on the exhaustiveness of diagnostic tests conducted, although it is also related to the geographic distribution of certain aetiologies(31).

According to data from the Spanish BE registry (RIBRON), the most frequent causes of BE in the adult population in Spain are previous respiratory infections (40%) and tuberculosis infection (13.5%)(32).

In these cases, the presence of bacterial infections triggers the inflammation and remodelling of the airway(33). In contrast, the alteration of systemic defence mechanisms characterizes primary immunodeficiencies, a less common but relevant aetiology(34).

Among these, humoral immunodeficiencies are notable, as, in the presence of deficient or altered immunoglobulin production, replacement therapy can reduce susceptibility to infections and minimize the risk of exacerbations and disease progression. For other immunodeficiencies, whether primary or secondary, prophylactic antibiotic treatments may be indicated to prevent opportunistic or potentially serious respiratory infections(34).

Another important cause of BE is primary ciliary dyskinesia (PCD), a genetic disease characterized by structural alterations in the cilia present on the surface of the respiratory epithelium. The normal function of cilia is to promote the upward movement of respiratory secretions, through synchronous motion and a characteristic pattern that allows mucus and trapped particles to reach the main bronchi and trachea for expulsion. In patients with ciliary dyskinesia, the motility of these cellular organelles is reduced or altered, leading to mucus accumulation, which favours inflammation and infections(35). Diagnosis is based on various tests that allow for the recognition of functional or structural alterations in the cilia. Although numerous responsible genes have been described, mutations cannot be identified in most patients, so genetic tests are often not used for diagnosis(36).

PCD is clinically characterized by recurrent respiratory infections and the development of BE during childhood, chronic rhinosinusitis, recurrent otitis, which may lead to hearing loss, and fertility issues. In some cases, congenital heart disease or situs inversus (which may be complete, in which case the disease is known as Kartagener syndrome) is associated. Non-respiratory manifestations are due to the presence of ciliated cells in other organs or systems, particularly in the reproductive system (Fallopian tubes and sperm flagella) and during early embryonic development, where they are called "nodal cilia" and play a role in polarizing cell migration, determining organ laterality(37,38).

Treatment for PCD is based on mechanical and pharmacological measures to increase secretion mobilization: respiratory physiotherapy, physical exercise, oral or nebulized mucoactive drugs. Currently, there is no specific treatment that can restore the normal function of cilia(39).

Autoimmune and autoinflammatory diseases can also be associated with BE, including rheumatoid arthritis, Sjögren's syndrome, and inflammatory bowel diseases. In this case, the primary trigger is the pro-inflammatory state typical of these diseases, whose control is essential to prevent respiratory disease progression(28,40,41).

Many other diseases are associated with the presence of BE: gastroesophageal reflux, allergic bronchopulmonary aspergillosis (ABPA), collagen diseases, obliterative bronchiolitis, non-tuberculous mycobacterial infections (NTM), congenital malformations, etc (42).

The management of BE, regardless of its aetiology, focuses on the prevention and treatment of infections, proper mucus clearance, and control of bronchial and systemic inflammation(43).

Currently, no drugs specifically developed for the treatment of BE has been approved, although a few molecules are currently undergoing phase 3 clinical trials or are already under evaluation by Regulatory Agencies, and scientific advances offer hope for new tools in the near future.

1.1.3 COPD

According to the most recent update of the international guidelines for the diagnosis and treatment of COPD(44), this disease is defined as "a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, expectoration, exacerbations) due to abnormalities in the airways (bronchitis, bronchiolitis) and/or in the alveoli (emphysema), which cause persistent airflow obstruction, frequently progressive"(44).

The latest national health report, published in 2023, records approximately 34 cases per 1000 inhabitants in the population over 40 years old in Spain, with a progressive increase in older age groups, reaching 78/1000 cases between 80 and 84 years of age. In 2019, nearly 14,000 deaths were attributed to this disease, which also represents a significant healthcare cost for the country(45).

In addition to the chronic symptoms of COPD, which, as the disease progresses, limit activities and worsen quality of life, exacerbations can occur, and their frequency and severity have a significant impact on patient prognosis and treatment.

The interaction between genetic and environmental factors lies at the root of the disease. The most important exposure factor is tobacco smoke, and in fact, most of the experimental

studies that have helped in understanding the pathophysiology of COPD have focused on smoking(46). On the other hand, in low-resource countries, exposure to biomass combustion products plays a significant role, accounting for up to 35% of cases(47). Recent studies also suggest a possible role of environmental pollution(48).

Among the genetic alterations, the only ones with a clear causal relationship with the development of COPD are mutations in the SERPINA1 gene, which cause alpha-1 antitrypsin (AAT) deficiency. AAT is the main antiprotease in the respiratory system, and its deficiency leaves the alveolar tissue unprotected and more exposed to protease damage(49). Recently, the involvement of various genetic and epigenetic alterations in the evolution of the disease has been proposed, but their role remains unclear(50,51).

A complex network of interactions contributes to the development of the disease, involving mechanisms such as hyperactivation of the innate and adaptive immune responses, the release of reactive oxygen species (ROS), and the imbalance between proteases and antiproteases(52).

Exposure to toxins triggers an unspecific inflammatory response, recruiting macrophages, neutrophils, eosinophils, and monocytes. Macrophages amplify the inflammatory cascade through the secretion of interleukins (IL-8 and IL-1), which attract more neutrophils responsible for producing ROS, neutrophil elastase (NE), and other proteases(52).

ROS can cause direct cellular damage, inactivate epithelial protection mechanisms, and cause hypertrophy and hyperplasia of mucus-producing cells, resulting in increased bronchial secretions(53).

The proteases produced by neutrophils, on the other hand, damage the alveolar tissue through proteolytic degradation, resulting in the development of emphysema. At the bronchial level, they can destroy ciliated cells responsible for proper mucociliary clearance. The damage from proteases is even more evident in patients with reduced or altered antiprotease production, such as in the case of AAT deficiency described earlier(54).

On the other hand, extracellular matrix degradation products induce lymphocyte differentiation, increasing CD8+ T lymphocytes. Activated CD8+ T cells release various harmful molecules, such as IFN-**γ**, tumor necrosis factor ⍺ (TNF⍺), IL-1, and proteolytic enzymes, which destroy structural cells through apoptosis or necrosis(55). Finally, the bronchial epithelium produces transforming growth factor beta (TGFβ), which promotes fibroblast and myofibroblast hyperproliferation, leading to airway remodeling and local fibrosis(56).

In conclusion, the interaction between various pathogenic mechanisms leads to structural damage at the alveolar, airway, and ciliated cell levels(46).

Changes in the small airway and emphysema, caused by the loss of alveolar elasticity, are responsible for the main functional alterations present in COPD patients: irreversible airflow limitation and increased airway resistance(46). These mechanisms prevent the lungs from emptying completely, resulting in static hyperinflation (i.e., during tidal breathing) and dynamic hyperinflation (during exertion or tachypnea). They also reduce inspiratory capacity. The clinical consequence is the progressive worsening of dyspnea in patients(57). Furthermore, the loss of gas exchange surface due to emphysema can lead, in the more advanced stages of the disease, to chronic respiratory failure due to insufficient oxygen delivery to the arterial system(58).

Excessive mucus production and its inadequate removal secondary to direct damage to ciliated cells lead to increased bronchial secretions, which contribute to accelerating functional decline and increase the risk of pneumonia(58).

In addition to respiratory changes, inflammation in COPD patients also extends to the systemic level, causing cardiovascular problems, sarcopenia, metabolic syndrome, and depression(59).

The treatment of COPD is based on the elimination of the pathogenic noxa, primarily focusing on smoking cessation, and the use of bronchodilators (BD) to control symptoms and slow disease progression. In more advanced stages, in patients with chronic respiratory failure, the use of O2 can improve quality of life and reduce mortality, while non-invasive ventilation can improve gas exchange in patients with chronic hypercapnia(60).

1.1.4 CHRONIC RHINOSINUSITIS

Despite involving the upper airways, CRS is not classically included in AWDs, and its diagnosis and care usually involve ear, nose and throat (ENT) specialists rather than pneumologists.

However, the frequent association of CRS with other AW conditions forces respiratory physician to deal with this condition on a regular basis. CRS prevalence in general population varies around 3-12% according to series (61–65), but it significantly raises in presence of other respiratory diseases: 22-45% in asthmatic patients (66), 6-50% in COPD (67–69), 50-90% in PCD (70,71) and 55-100% in adults with CF (72–74). Moreover, uncontrolled CRS has been correlated with poorer control of AWD in patients suffering from

both diseases, increasing the risk of exacerbation and aggravating lower AW symptoms(67).

The diagnosis of CRS requires the presence for at least 12 weeks of two or more key symptoms (nasal blockage/obstruction, nasal discharge, hyposmia, facial pressure/pain) combined with evidence of inflammation at nasal endoscopy or sinus CT, or with the presence of purulence from paranasal sinus or ostiomeatal complex(75).

Paranasal sinuses have mechanical, acoustical and thermic properties crucial for local homeostasis. Moreover, and most importantly from a respiratory perspective, they represent a first line of defence against microbes that could try to enter the respiratory system. From one hand, the presence of scattered cup cells and ciliated cells in sinus mucosa epithelium guarantees a mechanical barrier that traps microorganisms and noxious particles and prevent their penetration to the lower airways. From the other, sinonasal epithelium produces a variety of defence molecules in response to microbial invasion, such as enzymes, opsonins, defensins and endogenous antimicrobial molecules, that altogether initiate and maintain the inflammatory response.

In CRS, the imbalance in immune interaction between the host and the environment results in the alteration of these mechanisms (76). The presence of individual predisposition is essential in the development of the disease: in predisposed subjects, external triggers activate an aberrant innate immune response, that disrupts local homeostasis and prevents its restoration(77). Persistent inflammation causes mucosal oedema, which impairs mucociliary clearance and reduces the discharge of secretions. This creates a cycle where the inflammatory response is continually sustained, even in absence of triggers. The accumulation of mucus, combined with the heat and humidity within the paranasal sinuses, provides an ideal environment for the proliferation of pathogens(77).

From a molecular and pathophysiological perspective, CRS is a very heterogeneous disease, characterized by selective expression of Type 1 (T1), T2 or Type 3 (T3) immune responses and important geographical variations(78,79).

Various classifications have been identified and proposed; however similarly to asthma, two main clusters can be identified: T2 and non-T2.

For T2 endotypes, key players include IL-25, IL-31 and IL-33 that activate Type 2 innate lymphoid cells (ILC2). This activation promotes the polarization of the Th2 response, characterized by elevated levels of IL-5 and IL-4 (78).

T2 endotype is also characterized by increased production of IgE, responsible for mast cells activation, especially in nasal polyps(80).

Furthermore, the differentiation of monocytes/macrophage in type 2 (macrophages (M2), associated with tissue repair and fibrosis, leads to increased production of fibrin. Together with a downregulation of plasminogen, these mechanisms are responsible of tissue remodelling by retention of oedema and polyp formation(81).

In the non-T2 endotype, environmental triggers stimulate epithelial cells to secrete cytokines that promote the differentiation of Th1 and Th17 cells, leading to the development of neutrophilic inflammation. Activated Th1 cells produce high levels of IFN-γ, which contributes to cellular apoptosis, oxidative stress, and neutrophil chemotaxis. Additionally, Th17 cells produce IL-17A, TNF-α, and IL-22, further stimulating cytokine production and amplifying the neutrophilic inflammatory response. Moreover, neutrophils also produce TGF-β, which contributes to fibrosis and polyp formation (82,83). Similarly to what happens in BE, neutrophilic inflammation also leads to neutrophil extracellular trap (NET) formation, whose presence is associated with refractory CRS(84).

The importance of endotype identification has been progressively recognised in the last 10 years, as the presence of specific inflammatory pathways represents a promising target for biological treatment and might predict evolution and outcomes after surgery (85,86). However, they do not directly correlate with clinical phenotypes, as endotypes frequently overlap between different categories.

The most common classification of CRS depends on the presence (CRSwNP) or absence of nasal polyps (CRSsNP) (75).

CRSsNP is usually correlated with dental disease, ostiomeatal obstruction and presence of bacterial infection, while CRSwNP presents with nasal obstruction, olfactory impairment, responsiveness to corticosteroids and possible recurrence after surgery(87).

For many years, T2 inflammation has been considered predominant in CRSwNP, while non-T2 seemed to interest mainly CRSsNP. However, numerous studies contradicted this assumption, highlighting the importance of regional differences. In fact, T2 endotype is mainly present in CRSwNP in Western countries, while non-T2 endotype is more represented in CRSwNP in Asian populations and CF patients (88).

CRSwNP has been further subdivided into distinct subcategories based on specific clinical features, including the triad of aspirin sensitivity, asthma, and nasal polyps (Aspirin-Exacerbated Respiratory Disease - AERD); allergic fungal sensitization (Allergic Fungal

Rhinosinusitis - AFRS); central nasal involvement associated with allergic rhinitis (Central Compartment Atopic Disease - CCAD); and the presence of underlying systemic diseases such as CF, PCD, granulomatosis with polyangiitis (GPA), immunodeficiencies, and sarcoidosis(87).

CRS treatment is aimed at enhancing mucociliary clearance and sinus drainage to reduce inflammation. The keystones of treatment are topic steroids and nasal saline irrigation. Oral antibiotics can be used in case of bacterial infection, as well as antihistaminic drugs for allergic patients. In case of refractory T2 CRS, the use of biologic agents such as dupilumab, omalizumab and mepolizumab can be taken into consideration(89,90).

Endoscopic polypectomy can improve symptoms in CRSwNP; recurrence of polyps after surgery, however, is not infrequent and the risk should be assessed prior to surgery.

1.2 BAD THINGS COME IN PAIRS: BRONCHIECTASIS AND AIRWAYS COMORBIDITIES

BE is one of the most heterogeneous respiratory diseases. According to patients, most significant symptoms include management of secretions, fatigue, shortness of breath and cough, unspecific symptoms shared by most respiratory diseases(91). This may explain why, until just over a decade ago, many patients with BE were misdiagnosed and incorrectly labelled as having asthma or COPD, conditions that were far better recognized at the time.(92,93). Nowadays, thanks to years of efforts in BE investigation and education, awareness of the disease has increased exponentially, leading to a substantial rise in BE diagnoses due to more accurate diagnostic procedures.

While many questions about BE have been satisfactorily answered, one of the primary unresolved challenges in diagnosing and managing BE patients is the presence of respiratory comorbidities.

In the last decade, many authors have tried to define the prevalence and the characteristics of these associations. However, the lack of a consistent and reproducible definition of coexistence has led to significant variability in approaches, inclusion criteria, and methodologies across different studies, substantially affecting the reliability and comparability of the results.

1.2.1 WHY SHOULD WE LOOK FOR AW COMORBIDITIES IN BE?

The reasons for diagnosing AWD in BE patients include differences in clinical presentation, treatment complexities, impact on mental health, and bureaucratical considerations.

The presence of two or more AWD in the same patient seems to have a direct impact on severity of the disease, frequency of exacerbations and overall prognosis, regardless of which disease is considered the primary (94,95,104–110,96–103). The correct identification of AW comorbidities in BE patients allows better risk stratification and adequate clinical management.

Treatment represents probably the most relevant challenge of coexisting diseases in BE. On one hand, drugs that are commonly used in BE could be potentially contraindicated in presence of other conditions. It is the case of macrolides, that should be used with caution in patients at high risk for NTM infection (such as previous NTM infection, COPD or ICS use) to prevent the selection of antibiotic resistance(111–113). Similarly, nebulized antibiotics are discouraged in asthmatic patients due to the risk of inducing bronchospasm (43,114). On the other hand, the role of some treatments that well established in other respiratory diseases is still uncertain in BE due to lack of evidence, as it happens with BD and ICS. In particular, BD are not recommended in BE due to insufficient quality evidence (43,115,116), while there is still debate about the use of ICS in pure BE patients due to the risk of bacterial exacerbation (117,118) and NTM or fungal infection (119,120). Both treatments, however, remain indicated in cases of coexisting COPD or asthma, highlighting the importance of diagnosing underlying conditions to optimize patient management (43,121,122).

Another fundamental issue is the impact of chronic respiratory diseases on mental health. Patients often experience sadness, frustration, and anxiety, which can be exacerbated when multiple diseases are present, due to the increased complexity and symptomatic burden. In this context, the power of words and definitions is demonstrated: a correct diagnosis of comorbidities can empower patients and increase comprehension of symptoms through their inclusion inside a known and recognizable clinical entity. This can eventually lead to a more profound knowledge of their disease, increasing management skills and adherence to treatment (123,124).

Finally, the incomplete definition of comorbidities can hinder patient inclusion in clinical trials, affect medication reimbursement, limit access to social services and benefits, and more. This has a profound impact on patients' quality of life, potentially influencing their clinical status, access to healthcare resources, and treatment adherence.

For all these reasons, recognizing respiratory comorbidities in BE patients is crucial for both physicians and patients, and should be addressed at the earliest opportunity to prevent treatment delays(125).

BE and AWD have been the focus of numerous studies worldwide, both within BE populations and other AWD cohorts. Recently, two important papers were published analysing the prevalence and characteristics of asthma and COPD in the European registry, co-authored by the candidate. These results are commented in chapter 1.4.

1.2.2 BE AND ASTHMA

A complicated relationship develops between BE and asthma. While traditionally BE has been considered a neutrophilic disease and asthma an eosinophilic disease, this dichotomy has been eliminated by increasing evidences of the existence, in a significant proportion of patients, of distinct cellular phenotypes in both diseases.

In fact, in asthmatic patients conflicting evidence exists regarding the predominant endotype associated with BE: while most studies suggest an association between BE and neutrophilic asthma(25,126,127), a study of 200 patients with severe asthma found that BE correlated with a higher eosinophil count in peripheral blood(128).

Shared inflammatory pathways contribute to the coexistence of both diseases, though their causal relationship remains unclear. The point of closest contact is ABPA, a condition that can complicate both diseases. In ABPA, Th2-driven inflammation triggers or worsens bronchial dilatation, leading to excessive thick mucus production and bronchial inflammation in response to Aspergillus sensitization (REF). However, ABPA's pathophysiology is not a general model for the shared development of BE and asthma, as multiple mechanisms, only partially described, appear to be involved.

Identification of asthma in BE is challenging: no diagnostic criteria have been established yet, and asthma-like symptoms, such as wheezing, bronchospasm and sudden dyspnoea, are frequent in BE, especially during exacerbation and in response to nebulized antibiotic or saline solution(129–131). Also, hyperreactivity and reversibility to bronchodilators are not uncommon, with prevalence varying widely, reported in between 5% and over 35% of patients (132–135). Evidences also suggest the role of ciliary dysfunction in the development of hyperreactivity: mice with cilia deletion had higher levels of hyperreactivity and obstruction, without changes in mucus discharge or inflammation but increment in the expression of club cells, usually involved in tissue repair(136). Even response to non-specific provocation with methacholine or histamine has been reported in BE patients

without asthma(137,138). Although most of these studies mention the exclusion of asthmatic subjects, none provide details on the criteria used to diagnose clinically significant BE or clarify the asthmatic status of the patients involved.

Similarly, few studies have attempted to determine the prevalence of asthma in BE, but significant differences in definitions and inclusion criteria have contributed to extreme variability in the results, that range from 3 to 68% (Tab 1.1) (122,139–141).

According to these studies, asthma in BE patients was more frequent in female subjects (142), correlated with greater BE extension (141), more frequent exacerbations (96), worse lung function, lower rates of chronic bronchial infection (CBI) by any potentially pathogenic microorganism (PPM) and reduced use of inhaled antibiotics (142).

Tab 1.1: Studies investigating asthma in BE patients.

Author (year)	Country	N=	Criteria for asthma diagnosis	Asthma prevalence	Associated factors
Lonni(139) (2015)	Europe	1258	Reported	3.3%	NA
Note: EMBARC bronchiectasis registry; asthma reported by physician					
Kadowaki(143) (2015)	Japan	147	NA	7%	NA
Mao(96) (2016)	China	463	Symptoms + hyperreactivity	46.2%	More exacerbations
Note: Asthma diagnosis realized before the study. Hyperreactivity demonstrated with PBD, PEF variation or methacholine.					
Aksamit(144) (2017)	USA	1826	Reported	29%	NA
Note: USA bronchiectasis registry; asthma reported by physician					
Olveira (142)(2017)	Spain	2047	Reported	5.4%	More females, worse lung function, lower rates of CBI for any PPM, less inhaled antibiotics
Note: Spanish bronchiectasis registry (RIBRON); asthma reported by physician					
Mantyla(141) (2019)	Finland	95	Symptoms + hyperreactivity	68%	Greater BE extension
Note: asthma considered as BE aetiology when diagnosed before BE (26% of patients). Hyperreactivity demonstrated with PBD/PEF variation or methacholine.					
Dhar(145) (2023)	India	2195	Reported	23%	Lower mortality, less exacerbations, less hospitalizations
Note: Indian bronchiectasis registry (EMBARC-India); asthma reported by physician.					
Martinez-Garcia (2021)	Spain	1912	Reported	7.8%	More females
Note: Spanish bronchiectasis registry (RIBRON); asthma reported by physician.					
Moon(146) (2023)	Korea	598	Reported	22,4%	Higher BMI, greater sputum volume, lower FEV1, lower QoL, more previous pneumonia and measles
Note: Korean bronchiectasis registry (KMBARC); asthma reported by physician.					
Xu(147) (2025)	China	10324	Reported	5.4%	NA
Note: Chinese bronchiectasis registry (BE-China); asthma reported by physician. Slightly different prevalence between low-income (6.6%) and high-income regions (4.9%)					
Legend. PBD: Post-Bronchodilator; PEF: Peak Expiratory Flow; CBI: Chronic Bronchial Infection; PPM: Potentially Pathogenic Microorganisms; BE: Bronchiectasis; FEV1: Forced Expiratory Volume in 1 Second; QoL: Quality of Life					

In reverse perspective, BE in asthma have been object of numerous publications since the 1990s (148). The main reason is likely that bronchial dilatation observed in high-resolution computed tomography (HRCT) scans is a much more objective finding than any combination of signs and symptoms. In most cases, however, it has been considered the sole criterion for defining bronchiectasis, regardless of radiological extension of BE or the presence of a compatible clinical presentation. Also, only some of the studies specified the severity of asthma of the population analysed. This lack of homogeneity might explain the extreme variability of BE prevalence reported across all studies, ranging from 1% to 80% of the overall study population (Tab 1.2). However, the gap narrows when considering only severe asthma, with an average prevalence of approximately 35% (ranging from 16% to 67.5%) (107,110,128,149–154).

The presence of BE in asthmatic patients was frequently correlated with greater asthma severity(106,107,152–157), more frequent exacerbations and hospitalizations(106,150,158,159), worse lung function(110,157,160), longer disease duration (150,157,160) and use of inhaled steroids(159,160).

Only two authors reported radiological follow-up of their cohorts. Kurt observed a slight increase in BE prevalence at 6 years (15.2% vs. 13%), while Cukier unexpectedly found the opposite: of five baseline BE cases on HRCT, only two were confirmed after a year, with BE disappearing in two and reducing in one(161,162). However, the sample size is very small and insufficient to draw definitive conclusions.

Table 1.2: Studies investigating BE in asthma cohorts.

Author (year)	Country	N=	Asthma severity	BE prevalence	Associated factors
Paganin (1996) (155)		126	All/ unspecified	80,0%	Non-allergic asthma; greater severity
Grenier (1996) (156)		50	All/ unspecified	28,5%	greater severity
Park (1997) (157)		57	All/ unspecified	17,5%	Greater severity; longest duration; more severe obstruction
Cukier (2001) (162)		14	Persistent	36-21%	Unstable disease
Note: Comparison baseline and >1-year follow-up. BE in 5/14 patients; at FU resolved in 2 patients and decreased in 1 (2/14 vs 5/14)					
Takemura (2004) (163)	Japan	37	All/ unspecified	62%	Greater severity
Oguzulgen (2007) (106)		1680	All/ unspecified	3,0%	Greater severity; more hospitalizations
Note: severe asthma in 49% of patients with BE, while in 31% of pure asthmatics.					
Gupta(2009) (150)		463	Severe	40,0%	Longer duration; more hospitalizations
Bisaccioni (2009) (164)		245	All/ unspecified	26,8%	NA
Kurt (2009)		46	Mild and moderate	13/15.2%	NA
Note: 13% at baseline, 15.2% at 6 years follow-up					
Menzies (2011) [17]	Spain	133	Severe	35.3%	More severe obstruction; prevalence of Aspergillus
Lujan (2013) (165)	Spain	100	All/ Unspecified	12,0%	Age; longer duration; more severe obstruction; use of steroids
Note: Patients divided in Steroid-Dependent (SDA) and Non-Steroid-Dependent. BE in 20% of SDA group and 4% of NSDA group.					
Kang (2014)(159)		2270	All/ unspecified	2,2%	More exacerbations; use of steroids; ER visits
Dimakou (2017) (166)		40	Severe	67,5%	More use of ATB; sputum; chronic bronchial infection
Henkle (2017)(167)	UK	511/ 1,912	All/ unspecified	19/28%	NA
Weatherburn (2017)(168)		84505	All/ Unspecified	0,8%	NA
Coman (2018)(158)		184	Severe	47%	More exacerbations; presence of atopy; GERD; higher number of eosinophils

Padilla-Galo (2018)(107)	Spain	398	All	28.4%	Sputum production; greater severity; lower FeNO values
Kim (2018) (152)		91	Severe	35,2%	Greater severity; age; lower FEV1; female sex
Heffler (2019) (153)		437	Severe	16%	Greater severity; more exacerbations and hospitalizations; severity of obstruction
Garcia-Clemente (2020)(154)	Spain	108	Severe	35%	Age; duration of the disease; greater severity; more hospitalization; severity of obstruction
Xie (2019) (169)		2207	All/ unspecified	19.7%	Haemoptysis; more exacerbations; more sputum production; more hospitalization
Frossing (2022) (149)		108	Severe	31%	More sputum: higher eosinophil count and degranulation;
Legend: BE: Bronchiectasis:; FU: follow-up; ER: Emergency Room; ATB; Antibiotic Treatment; GERD: Gastroesophageal Reflux Disease; FeNO: Fractional Exhaled Nitric Oxide; FEV1: Forced Expiratory Volume in 1 Second; QoL					

Considering that CT scans are not usually included in the follow up of asthmatic patients, in clinical practice it is crucial to identify subjects at higher risk of developing BE.

Research efforts have been made to identify risk factors for BE in moderate-to-severe asthma. Some evidences suggest a role of humoral immunity, considering the increased frequency of BE in asthmatic patients with hypogammaglobulinemia(170); this is not surprising, as primary immunodeficiencies are a well-known cause of BE.

Padilla-Galo and colleagues investigated clinical factors correlated with BE in asthma in order to create a scoring system to assess the risk for BE development, the NOPES score. It includes four variables: FeNO >20.5 ppb, Pneumonia, Expectoration and asthma Severity, reaching an area under the curve (AUC)-ROC of 70% and a specificity of 95%(107).

In conclusion, data about the coexistence of asthma and BE are limited and significantly impacted by the lack of standardization in definitions and methods. This inconsistency leads to variations in patient selection and risk of multiple biases.

1.2.4 BE AND COPD

Despite some common clinical features, such as the presence of chronic cough and dyspnoea, BE and COPD differ significantly in many aspects. From a diagnostic point of view, while BE requires radiological evidences and clinical symptoms, the diagnosis of COPD is based on the spirometric evidence of bronchial obstruction (171,172). Even if non-reversible airflow obstruction can be present in BE patients and is recognized as a severity marker (173), severity of the disease is not necessarily proportional to obstruction degree (174). In contrast, in COPD lung function represent one of the main features to stratify severity and prognosis, together with frequency of exacerbation (175).

Lastly, risk factors for the two diseases also differ significantly: COPD primarily develops due to exposure to toxic inhalants, such as tobacco smoke and biomass fuels, whereas BE has a diverse range of risk factors, including COPD itself (REF). The causal relationship between the development of BE and COPD is unclear and possibly bidirectional. On one hand, it is clear how smoking and toxic exposures can impair mucosal immunity mechanisms, leading to inflammation and increased susceptibility to infections that can result in bronchial remodelling and BE development (see chapter 1.1.3)(176). On the other hand, experimental data suggest a role of NE in promoting smoke-induced bronchial damage, a mechanism that could be increased in BE patients, considering the elevated levels of NE that characterize the disease(177). Moreover, intriguing data indicate that neutrophilic inflammation, mucin expression, and microbial composition differ between patients with comorbid COPD and BE and those with only one of the conditions. Microbiome of patients with BE and comorbid COPD/BE are more similar compared to COPD ones, suggesting that bronchial dilatation may not be a mere consequence of COPD progression, but could represent a distinct endotype with potential clinical implications yet to be explored(178,179).

Similarly to asthma, epidemiology of the association between BE and COPD is flawed by lack of reproducibility between different studies, leading to significant variability in the reported prevalence of BE among COPD patients and COPD in BE cohorts.

In fact, studies available in literature differ in inclusion criteria, radiological techniques (HRCT vs normal CT scans), severity of the primary disease and definition of BE.

The inclusion of COPD patients not presenting typical BE symptoms can result in overdiagnosis of BE, as asymptomatic bronchial dilatation are reported in up to 30% of healthy subject over 40 years of age (180,181). Conversely, the use non-high-resolution CT may negatively impact BE prevalence estimates, as the lower image resolution may be

insufficient for a comprehensive bronchial enlargement assessment. Moreover, the presence of COPD could impact in BA ratio due to changes in vessel diameter, especially in more severe patients. Hypoxic vasoconstriction reduces arterial diameter, artificially increasing BA ratio and potentially leading to the overdiagnosis of BE. Vice versa, in the presence of pulmonary hypertension, an increased vessel diameter may lower the BA ratio, resulting in the underdiagnosis of BE(182–184).

Few series explored the presence of COPD in BE patients, with a reported prevalence of 8.8-66.2%. Most of these papers report prevalence of COPD from regional or national BE registries, where the comorbidity is reported either from physicians of patients, limiting the possibilities of confirming the criteria used for the diagnosis.

BE patients with COPD were more likely to be older males with greater disease severity. They typically had lower lung function (185,186), higher mortality rates(185,187), more frequent exacerbations and hospitalizations(187,188), increased use of inhaled treatments(185,186), and a greater symptom burden(185,186).

On the other hand, the presence of BE in patients with a primary diagnosis of COPD has been object of numerous studies(103,189–193). Despite the wide prevalence range (4% to 72%, with a median of 27% and a mean of 33%) due to the lack of homogeneity previously discussed, most studies agree that patients with COPD who present with bronchial dilatation exhibit worse clinical features.

Evidence of BE in COPD is associated with increased risk of exacerbation(103), isolation of PPM (103,192,193), severe airway obstruction(103,191), mortality, increased sputum purulence(191). Interestingly, some authors have reported a history of lower tobacco consumption, both in pack-years and overall smoking history(189,193).

In short, patients with COPD and BE appear to have more severe disease and worse prognosis, regardless of the primary disease. However, lack of standardization in the definition of both diseases in different studies rases concerns about diagnostic accuracy and clinical implications.

1.2.5 BE and CRS

Since the second half of the XIX century, when otorhinolaryngology and pneumology developed as individual specialties, upper and lower airways have been treated and studied separately(194). However, the respiratory tract is constituted by sequential structures lined by a continuous ciliated epithelium, sharing similar pathophysiological mechanism. This concept is at the base of the “Unified airway hypothesis”: proposed at the end of the 90es,

it is now a well-established model supported by functional, pathological and immunological evidences especially in asthma and allergic diseases (195,196). As a logical consequence of this model, it is worth considering the potential impact of CRS on the lower airways and whether the presence of BE may influence the clinical course of upper airways diseases. CRS is a well-known comorbidity in PCD and CF: both ciliary dysfunction and alterations in mucus lead to impaired mucociliary clearance and upper airways chronic inflammation and infection(197,198). However, its prevalence and pathophysiology in BE due to other aetiologies it is less clear. Some series observed an increased prevalence in patients with idiopathic BE compared with post-infectious. This might reflect a different degree of inflammation, more distributed through the entire airway epithelium in the first case, localized to the site of infection in the second one (31,199,200).

The presence of CRS in BE has been linked to a predominant Th2 inflammatory profile, marked by eosinophilia, elevated IgE levels, and a higher prevalence of asthma(99). This association is well recognized and not unexpected, even in patients with a primary diagnosis of BE. However, a 2024 study offered a nuanced perspective, showing that CRS, whether with or without nasal polyps, was associated with airway eosinophilia but not with asthma. Interestingly, most patients in that study had negative results on instrumental asthma tests, including methacholine challenge, suggesting that eosinophilic inflammation in BE-CRS may occur independently of clinical asthma (201). Also, BE patients with and without CRS presented no differences in bronchial microbiome composition, but showed differences in the interactions between aerobic and anaerobic bacteria and had distinct nasal microbiome(201). These results support the idea of the existence of a distinct endotype characterizing patients with BE and upper airway involvement.

According to available series, the prevalence of CRS in BE patients varies from 7 to 75% of patients(89,101,200,202–206). Once more, diagnostic criteria vary: some authors base the diagnosis solely on clinical symptoms, while others require radiological or endoscopic evidence of sinus inflammation, in accordance with the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) guidelines(207).

While data about the impact on lung function are contrasting and inconclusive, patients with both diseases show greater radiological severity of BE(206), lower quality of life(206,208). and more exacerbations(98–101) than patients without upper airways involvement.

Data from the European bronchiectasis database (EMBARC) were presented at 2018 European Respiratory congress. The analysis involved 10920 patients, showing a

prevalence of 20.7%. CRS was associated with better lung function, worse respiratory symptoms, more frequent moderate exacerbations but less hospitalization(209).

Clinical implications of the coexistence of CRS and BE have been also reported in relation to treatment. From one side, endoscopic sinus surgery has shown to reduce the symptoms of BE and frequency of bronchial exacerbations(210,211). On the other hand, some studies observed a reduction of CRS symptoms with long term macrolides treatment(212,213), a cornerstone of BE treatment, even if contrasting evidences exists on this matter(214,215).

CRS seems to have a role also in BE development: evidences suggest that the presence of CRS is a risk factor for posterior development of BE, with an average latency of around 6 years(216).

In summary, despite its prevalence, the association between CRS and BE is less recognized compared to other airway comorbidities of BE, likely due to the division of upper and lower airway management in both research and clinical practice. However, data suggest a reciprocal impact between upper and lower airway involvement in BE, driven by mechanisms that remain to be described and that lead to significant clinical implications.

1.3 DEFINING COPD AND BE COEXISTENCE: THE ROSE CRITERIA

While reviewing the existing literature on BE and airway comorbidities, it becomes evident how the definitions used for each disease, which vary among authors, significantly impact on the reported data. Establishing clear criteria and definitions would not only enable more precise data collection and comparison but also standardize the identification of specific subgroups of patients for inclusion or exclusion in clinical trials and for regulatory purposes, such as drug reimbursement.

On an attempt of defining the association of BE and COPD, in 2019 the EMBARC Airways Working Group (AWG) launched a Delphi survey to establish a consensus definition of the association that could be simple, clear, and easy to use. The work was coordinated by the candidate, who is the first author of the paper presenting the results.

Delphi method is a consensus-building approach used when scientific evidence is insufficient, limited, or conflicting. It is based on four key principles: (1) Anonymity, ensured by a single moderator collecting responses; (2) Iteration, with repeated rounds of questioning until response stability is reached; (3) Controlled feedback, where participants

review previous responses before proceeding; and (4) Statistical group response, analysed through central tendency and frequency distributions(217).

This method allows the collection of expert opinions without requiring face-to-face meetings. Additionally, iterative discussions within the panel help enhance validity and reduce methodological biases(217).

The Delphi survey for the definition of COPD-BE association was developed by a panel of 16 experts in COPD and BE from the EMBARC AWG, including a small group of radiologists specialized in thoracic imaging.

To ensure a diverse representation of opinions while adhering to Delphi method recommendations, the panel selected participants based on gender, geography, and expertise in COPD, BE, or thoracic radiology. Participants were asked to grade a list of 35 statements divided into 5 categories (clinical, functional, microbiological, radiological and pathophysiological features) from 0 (completely disagree) to 9 (fully agree).

A total of 102 experts from across Europe responded to the first round of the survey. This was followed by a second round, which included only the 16 statements that had reached a positive or negative consensus, aiming to achieve further reiteration, and two additional open questions to further explore participants opinions. The 83 responders confirmed the answers of the first round, with higher levels of concordance.

The process led to the identification of four items considered necessary to define the COPD-BE association: 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. These criteria can be summarised in the acronym ROSE (radiology, obstruction, symptoms, exposure) (Fig. 1.1) (218).

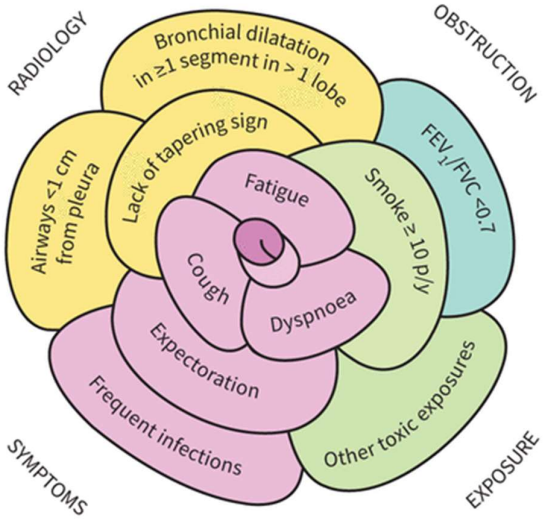


Figure 1.1 ROSE criteria for the diagnosis of BE-COPD association (from Traversi et al., EJOR 2021 (217).

Since their publication, ROSE criteria have been validated in both COPD(219) and BE(220) cohorts, and have been used in studies involving COPD-BE patients(221–

226). We hope this definition will help improving the knowledge and management of COP-BE association in the future.

1.4 EMBARC REGISTRY: TURNING THE TABLE

The EMBARC registry is one of the pioneering BE registries (following the Spanish registry, the first of its kind) and is currently the largest BE registry globally. It serves as a valuable data source, has driven significant advancements in disease research and has inspired the establishment of other international registries worldwide.

It enrolled almost 17.000 patients from 28 European Countries with CT confirmed bronchiectasis, from 2015 to 2023. Patient characteristics and clinical data of the disease were collected annually using a standardized case report form for a maximum of 5 years(227,228).

Several analyses have been conducted using registry data. Among them, the investigation of the prevalence and outcomes of asthma and COPD stands out as particularly valuable, offering significant insights beyond previous knowledge. Both analyses included 16,963 patients, enrolled between January 2015 and April 2022. Asthma and COPD in EMBARC database can be registered in two different fields, as a comorbidity or as the aetiology of BE. For the purposes of these analysis, the two definitions have been considered together, as outcomes asthma and COPD reported as comorbidities or aetiology did not show significant differences.

The large sample size and the representation of patients from across Europe are two key strengths of the studies that will be presented at continuation. However, the retrospective design and the lack of a clear definition for the asthma-BE association are notable limitations.

To address the many uncertainties surrounding BE and airway comorbidities, further prospective, comorbidity-focused studies are essential.

1.4.1 BE AND ASTHMA IN THE EUROPEAN REGISTRY

Clinicians reported a diagnosis of asthma in 5,267 of the 16,963 included in the cohort (31%). Patients with BE+asthma were younger, more likely to be females and never smokers, had higher BMI and higher prevalence of concomitant CRS (27.2% vs 17.5%) and nasal polyps (12.5% vs 4.8%). They presented more severe respiratory symptoms and lower quality of life compared with patients without asthma. Nevertheless, severity of BE, expressed with the Bronchiectasis Severity Index (BSI), was significantly lower in this group.

Lung function values between the two groups did not show important differences, while treatment burden was significantly higher in patients with BE+asthma. In particular, these patients were treated with more ICS, bronchodilators, airway clearance, long-term macrolides, and other prophylactic antibiotics. However, despite the diagnosis of asthma, 19.7% of patients were not receiving ICS. A smaller group of patients was treated with chronic oral corticosteroids (OCS) (7.8%) or monoclonal antibodies (1.1%).

Microbiological differences were observed between the two groups, with similar rates of PA infection in patients with comorbid asthma but higher prevalence of *H. influenzae, M. catarrhalis, and S. pneumoniae*. These differences were not associated with increased exacerbation rates.

Surprisingly, the analysis of ICS effect showed it was associated with reduced risk of hospitalization in both groups, with and without asthma, while patients with BE+asthma not receiving ICS had increased risk of hospitalization and did not show reduction in mortality. It is possible that the lower mortality risk in patients with BE and asthma treated with ICS is due to better disease control through the management of asthma-related airway inflammation.

Geographical variations in asthma prevalence were observed, aligning with the known epidemiology of asthma in the general population, more common in Northern Europe. However, differences in the diagnostic tests used**,** which are not recorded in the database**,** could vary across European regions, potentially influencing the reported prevalence rates.

The lack of standardization on diagnostic tests represents an important limitation of the study: tests specifically used for the diagnosis and the follow up of asthma, such as post-bronchodilator (PBD) test, methacholine and FeNO, are not recorded in EMBARC database. Even for variables that were collected, such eosinophil and IgE levels, data are reported for only a limited subset of patients.

In conclusion, this study highlights that asthma is a common comorbidity in BE patients across Europe. Patients with both BE and asthma should be considered a high-risk group, with a higher burden of symptoms and frequent exacerbations, requiring personalized follow-up and appropriate ICS treatment, which is associated with lower mortality and a reduced risk of severe exacerbations. However, these conclusions should be interpreted with caution, as the diagnosis of asthma in the database is based mostly on the judgment of individual investigators and only rarely on diagnostic procedures and could not be confirmed using the currently available variables, even if standardized criteria were defined. (122).

1.4.2 BE AND COPD IN THE EUROPEAN REGISTRY

Among the 16,963 patients included for the analysis, 4,324 had a physician-reported diagnosis of COPD (25%). This cohort, compared with patients without COPD, exhibited several significant differences. Patients with COPD were older, more likely to be male, had a higher BMI and greater comorbidity burden.

Although radiological severity was only slightly higher, with a greater involvement of the lower lobes, patients with COPD experienced more severe disease overall. They had higher Bronchiectasis Severity Index (BSI) scores, worse quality of life and symptom burden, and a higher frequency of moderate and severe exacerbations. Dyspnoea severity, measured by the mMRC score, was greater, and lung function was more impaired.

Inhaled treatments, long-term oxygen therapy, and non-invasive ventilation were more commonly used in this group, while airway clearance techniques and inhaled antibiotics were prescribed less frequently. However, *Pseudomonas aeruginosa* (PA) infection was slightly more prevalent among patients with COPD, as were infections with *Moraxella catarrhalis*, enteric gram-negative organisms, *Streptococcus pneumoniae*, and *Stenotrophomonas maltophilia*. In contrast, *Staphylococcus aureus* was reported less frequently in this group compared to patients without COPD.

The same analysis was then repeated applying the ROSE criteria to establish objective diagnosis of COPD in patients where information about lung function and pack-year smoking was available (15,231 patients), with very interesting results.

According to the ROSE criteria, COPD was confirmed in only 55.6% of patients with a physician-reported COPD diagnosis, while 7.7% of those previously classified as COPD-negative also met the ROSE criteria. Combining both groups, ROSE-confirmed COPD was identified in 3,007 patients, representing 17.7% of the cohort.

Among those with a reported COPD diagnosis, 22.1% did not meet the functional criteria, having an FEV1/FVC ratio >70%, while 30.8% had a smoking history of ≤10 pack-years. Overdiagnosis was more prevalent in certain countries, particularly Romania (40%), Ukraine (32%), and Macedonia (23%). This could reflect differences in standards of care in Eastern Europe, or other factors such as a higher prevalence of noxious exposures other than tobacco, which were not accounted for in the analysis.

Patients were then categorized into four groups based on their reported COPD status and ROSE classification: COPD+/ROSE+, COPD-/ROSE+, COPD+/ROSE-, and COPD-/ROSE-.

A clear downward trend in markers of disease severity (dyspnoea score and FEV1) was observed across these groups. Patients in the COPD+/ROSE+ group had the most severe clinical presentation and poorest outcomes, including higher mortality, exacerbation rates, and hospitalization risk. Notably, patients with a reported COPD diagnosis but who did not meet ROSE criteria still exhibited similar clinical characteristics, whereas those without a COPD diagnosis had a better overall clinical status, regardless of ROSE classification. These results suggest that the COPD label might be assigned to patients because of higher severity of their disease instead of a clinical COPD diagnosis.

This study confirms a more severe disease in patients with COPD-BE association in a large international cohort and emphasizes the necessity of applying objective criteria to accurately define the relationship between BE and COPD. Implementing the ROSE criteria more broadly could help minimize inconsistencies in COPD diagnosis, ensuring it is not misapplied to bronchiectasis patients without relevant exposures or airflow obstruction(121).

2. RATIONALE AND HYPOTHESIS

2.1 RATIONALE

BE is a chronic airway disease of growing clinical relevance, with a significant impact on patients' QoL and still limited therapeutic options. Although for a long time it was considered a rare and orphan condition, the efforts of the international medical community have demonstrated that its prevalence is much higher than previously estimated. In the past two decades, knowledge about BE has expanded substantially, covering pathophysiological mechanisms, clinical characteristics, the identification of phenotypes and endotypes, and the development of targeted pharmacological treatments.

Despite these advances, several aspects of BE remain poorly understood. Among them, the relationship between BE and other AWDs is one of the poorly investigated areas. Data from clinical series and national and international registries show that a significant proportion of patients with BE also present with at least one additional AWD. This highlights the clinical importance of systematically assessing these conditions, as their coexistence can influence outcomes, QoL, and response to treatment.

However, the considerable heterogeneity of BE, the frequent symptoms overlap with other conditions such as asthma, COPD, and CRS, and the absence of standardized approaches for their diagnosis within the context of BE, greatly affect the way these comorbidities are identified, reported, and managed.

2.2 HYPOTESIS

We hypothesize that a systematic and complete assessment of the airways in patients with bronchiectasis allows the identification of phenotypic differences between patients with isolated BE and those with coexisting AWDs (e.g., asthma, COPD, CRS).

Also, the systematic assessment of upper and lower airways in patients with BE will make it possible to identify key variables useful in formulating **specific diagnostic criteria** for asthma and CRS in BE.

We further hypothesize that integrating such assessments into routine clinical evaluation will improve the diagnostic accuracy for comorbid AWDs and support a more personalized and effective clinical management strategy.

3. AIMS AND OBJECTIVES

3.1 AIMS OF THE STUDY

This study aims to conduct a comprehensive assessment of both the upper and lower airways in patients with BE, to demonstrate the existence of phenotypic differences between individuals with isolated BE and those with associated AWDs.

Expanding the conventional clinical and instrumental work-up could allow the identification of clinical, functional, or radiological variables not currently considered in standard follow-up, which may raise clinical suspicion for underlying or associated comorbid AWDs and improve the overall clinical management of BE patients.

3.2 PRIMARY OBJECTIVE

- To identify and characterize distinct clinical, functional, radiological, and inflammatory airway characteristics in a cohort of patients with BE with no previously diagnosed AWDs. This will be achieved through the integration of non-conventional diagnostic tools, including extended lung function testing, inflammatory biomarkers, detailed radiological assessment, clinical signs and symptoms of asthma, COPD, and CRS, and standardized quality of life measures.

3.3 SECONDARY OBJECTIVES

- To determine the prevalence of coexisting asthma, COPD, and CRS in patients with BE with no previously diagnosed AWDs.
- To assess the applicability and validity of asthma and CRS diagnostic criteria, originally developed for the general population, when applied to patients with BE.
- To evaluate the utility of disease-specific questionnaires for BE and other AWDs in increasing clinical suspicion of airway comorbidities, based on patient-reported outcomes, and to investigate how questionnaire results correlate with clinical presentation and disease severity.

4. METHODOLOGY

4.1 STUDY DESIGN

We conducted a prospective observational monocentric study.

The study was approved by the Hospital Vall d'Hebron (HVH) Ethical Committee with the code PR(AMI)154/2019.

Participants were enrolled from the BE outpatient clinic of the HVH, Barcelona, from March 2023 to February 2025. Before enrolment, patients were extensively informed of the study procedures, potential risks and expected benefits, and informed consent was collected before any assessment was performed.

Patients' visits were performed in the HVH Pneumology department according to best practice guidelines (BPG) and local guidelines.

Each patient received a unique identification code; data were codified and then collected in a RedCap database, in accordance with applicable Data Protection Laws. Only members of the study team had granted access to the database.

4.2 STUDY PARTICIPANTS

4.2.1 INCLUSION CRITERIA

- Written informed consent must be obtained before any assessment is performed.
- Male and female patients of ≥ 18 years of age at enrolment.
- Proven diagnosis of non- cystic fibrosis (CF) BE as documented by CT scan AND the presence of compatible clinical symptoms as recorded by the attending physician.

4.2.2 EXCLUSION CRITERIA

- Patients with CF (to exclude according to British Thoracic Society guidelines for non-CF bronchiectasis)(229).
- Patients with a primary diagnosis of bronchial asthma or COPD, diagnosed by the attending physician, or with active ABPA
- Any other significant medical condition that is either recently diagnosed or was not stable during the last 3 months, and that in the opinion of the investigator makes participation in the trial against the patients' best interests.

- Patients with active tuberculosis
- Patients currently receiving treatment for NTM pulmonary disease.

4.3 STUDY PROCEDURES

4.3.1 SUMMARY OF THE PROCEDURES

After evaluation of inclusion and exclusion criteria, patients were contacted for study proposal, and a visit was scheduled to perform study procedures, including: clinical visit with collection of standardized information about AWD, administration of questionnaires, spirometry with bronchodilation test, plethysmography, diffusing capacity of the lung for carbon monoxide (DLCO), blood samples for complete blood count (CBC), Immunoglobulin E (IgE) measurement and allergy assessment through Phadiatop® panel, FeNO, sputum culture.

4.3.2. BE, ASTHMA, COPD AND CRS DATA COLLECTION:

Data were collected through a standardized interview based on validated signs and symptoms questionnaires, if available, or with a specific case report form designed according to literature.

Specific quality of life questionnaire for BE, asthma and COPD were administered to all patients independently from the presence or absence of AW comorbidities. Patients were instructed on completing each questionnaire referring to their respiratory condition in general, without considering the disease indicated in test's description.

Variables collected included:

- Description of the population
  - ✓ Demographic data
  - ✓ Non respiratory comorbidities
  - ✓ Non respiratory treatment
- BE characterization
  - ✓ Aetiologies
  - ✓ Signs and symptoms (Cough by Leicester Cough Questionnaire (LCQ), Self-reported presence, volume and colour of sputum (Murray scale) after a 24hours

collection of expectorated sputum in a standard 120ml container for biological samples, dyspnoea (mMRC scale))

- ✓ Rate of BE exacerbations in the previous year as per Hills Criteria(130).

- Respiratory treatment
  - ✓ Current respiratory treatment (particularly long-acting antimuscarinic agents LAMA, LABA, ICS, LABA/ICS combinations, Anti-leukotrienes, long term oral corticosteroids (OCS), long term macrolides, long term inhaled antibiotics)
  - ✓ Specific treatments for acute phases in previous year (cycles of antibiotics, cycles of OCS)
  - ✓ Pulmonary rehabilitation
  - ✓ Regular or recurrent physiotherapy
- Asthma clinical evaluation

History of asthma symptoms (Questionnaire based on Global Initiative for Asthma(GINA) ERS list of symptoms (14).

- ✓ Wheezing and chest tightness (frequency in the previous month)
- ✓ Family history of asthma (parents, brothers/sisters, and descendants)
- ✓ Current environmental exposure to inhalant (pets, second hand smoke, hazardous dusts in the workplace: mineral, metallic, chemical or vegetable dusts, sprays, mists, smokes, fumes, molds and spores).

- COPD clinical evaluation
  - ✓ History of tobacco use.
  - ✓ History of long-term professional/environmental exposure to noxious particles: There is no consensus on which occupational exposures are definitively linked to chronic respiratory diseases, nor is there standardization regarding the duration of exposure(230). For our study, a positive history of potentially disease-causing exposures was defined as at least 10 years of work in environments with known exposure to organic or inorganic dust, noxious gases, chemicals, pesticides, or similar agents, without adequate respiratory protection(231,232). Additionally, exposure to biomass for 10 or more years was also considered positive exposure.

Doubtful cases were evaluated individually, and the variable was recorded based on the researcher's judgment.

- CRS clinical evaluation
  - ✓ Symptoms and signs questionnaire
  - ✓ Previous sinus surgery
- Quality of life assessment through specific questionnaires:
  - ✓ Saint George Respiratory Questionnaire(233) (SGRQ)
  - ✓ Asthma Control Test (ACT)
  - ✓ COPD Assessment Test (CAT)
  - ✓ Sinonasal Outcome Test 22 (SNOT-22)

4.3.3. FUNCTIONAL ASSESSMENT

- Global spirometry (slow and forced flow-volume curve) plus bronchodilator test (after long-acting bronchodilator withdrawal of 48 hours at least), as European Respiratory Society (ERS) and American Thoracic Society (ATS) Task Force(234)
- Plethysmography
- DLCO

4.3.4 INFLAMMATION AND MICROBIOLOGY ASSESSMENT:

- Complete blood count. In case of eosinophilia (eosinophils > than 300/mm^3), other causes according to patient clinical presentation and history. If the patient with eosinophilia travelled or lived in endemic area for strongyloids, coccoidomycos and other parasites (the most inlands in tropics and sub-tropics), faeces microscopy x3 for parasites and serology for strongyloides were added (235).
- IgE in peripheral blood were measured.
- Measure of fractional exhaled nitric oxide (FeNO) (ATS/ERS guidelines 2005(236)). A cut off value of 25ppb was considered suggestive of asthma (both confirmed and possible) according to ATS clinical practice guideline and current literature on asthma in bronchiectasis patients (107,237,238).

- History of chronic bacterial infections was recorded, as well as sputum cultures in stable state from the year preceding enrolment. When possible, a sputum sample was sent for bacterial, mycobacterial and fungal culture.

4.3.5 ALLERGY ASSESSMENT

- Blood screening was performed with Phadiatop panel (specific IgE for a mixture of representative allergens, including grasses, trees, weeds, cat, dog, mites and molds).

4.3.6 RADIOLOGICAL CHARACTERIZATION

- The most recent HRCT scan available within the 5 years before the inclusion was included in the analysis. If no computed tomography (CT) was available within this timeframe, a new control has been performed.
- A radiologist specialized in thoracic imaging reviewed the available studies and reported the following parameters:
    - Severity of BE following the modified Reiff score: lungs are divided in three lobes each (with lingula considered as a separated lobe); each lobe is graded according to the presence and degree of bronchial dilatation: no bronchiectasis=0, cylindrical = 1, varicose = 2, and cystic = 3. The final score is determined by the sum of the 6 lobes, ranging from 1 to 18.
    - Presence/absence of cystic BE
    - Presence/absence of emphysema
    - Presence/absence of bronchial wall thickening (BWT)
    - Presence/absence of mucus plugging (MP)
    - Presence/absence of ground glass opacities (GGO)
    - Presence/absence of air trapping (if expiratory phase available)

4.3.7 ADDITIONAL PROCEDURES/DATA COLLECTION

- Methacholine challenge test: it was not possible to realize methacholine challenge tests to patients as per original protocol. However, data were collected about previously performed methacholine tests if available.
- Nasal endoscopy and sinus CT: In selected patients with symptoms of CRS, nasal endoscopy or sinus CT scan were performed to assess tissue inflammation and the presence of nasal polyps, according to clinical need and at investigators discretion. These procedures were also recorded if had been realized up to a year prior to inclusion, at a stable state.

4.4 WITHDRAWAL OF PARTICIPANTS FROM STUDY

Each participant had the right to withdraw study at any time. In addition, the investigator could discontinue a participant from the study at any time if he or she considered it necessary for any reason. The reason for withdrawal was be recorded in the CRF.

If the participant was withdrawn due to an adverse event, the investigators arranged follow-up visits or telephone calls according to patients' needs.

4.5 SOURCE DATA

Source documents are original documents, data, and records from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication were summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, radiographs, and correspondence.

An online CRF in the platform RedCap was compiled for each participant, containing subject identification, any correspondence, along with data obtained throughout the study and details of each visit.

All documents were stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant was referred to by the study participant code, not by name.

4.6 STATYSTICAL ANALYSIS

4.6.1 DATA ANALYSIS

Categorical variables are presented as percentages, while continuous variables are presented as means and medians, standard deviations (SD), or interquartile ranges (IQR), as appropriate. The normality of the distributions was assessed using the Kolmogorov–Smirnov test.

Sociodemographic and clinical characteristics were compared based on certain variables of interest. For quantitative variables, Student's t-test (or Mann–Whitney U test when normality could not be assumed) or ANOVA (for variables with more than two categories) (Kruskal–Wallis test in case of non-normal distributions) were applied. The Chi-square test (or Fisher's exact test for frequencies <5%) was used to compare categorical variables. The linear relationship between quantitative variables was assessed using Pearson's test or its non-parametric version (Spearman's test).

A multivariate model was developed using a backward stepwise logistic regression model, considering asthma diagnosis as the dependent variable. Independent variables with a significance level of <0.2 in the univariate analysis were included. The results were expressed as odds ratios (OR), 95% confidence intervals (CI), and p-values. To evaluate the overall fit of the model, the Hosmer–Lemeshow goodness-of-fit test was performed.

For all tests, p-values <0.05 were considered statistically significant, and all analyses were conducted using version 4.2.1 of R (R Foundation for Statistical Computing).

4.6.2 DEFINITION OF BE AIRWAYS COMORBIDITIES

For defining different airway diseases, a disease-specific approach was applied.

- **ASTHMA**: was characterized based on the clinical, functional, and biological criteria outlined in the GINA guidelines. Given the varying significance of each criterion within the GINA definition, a standardized approach was adopted by categorizing variables into major (characteristic symptoms, functional findings) and minor criteria (family history, presence of allergies, elevated FeNO, blood eosinophilia). These criteria were then combined to stratify the likelihood of an asthma diagnosis (Tab. 4.1).

Table 4.1 Classification of criteria and evaluation of asthma component	
4.1.1 Classification of asthma criteria	
Major criteria	CLINICAL FINDINGS - Characteristic symptoms in the past
	FUNCIONAL FINDINGS - Positive BD, positive Methacoline test, PEF daily variability> 10% (F)
	BIOLOGICAL FINDINGS - none
Minor criteria	CLINICAL FINDINGS - family history, aspirin intolerance, atopy (defined as positive Phadiatop)
	FUNCIONAL FINDINGS - none
	BIOLOGICAL - inflammatory sputum profile (both eosinophilic or neutrophilic); FENO value>25ppb, Blood eosinophilia
4.1.2 Patient Stratification according to the likelihood of asthma	
Combination of: 1 clinical major crit. AND 1 functional major crit. AND 1 biological crit.	**Confirmed asthma**
Combination of: At least one clinical OR functional Major criterion ± 1 minor	**Possible asthma**
No major criteria	**No asthma**

- **COPD**: ROSE criteria for the definition of BE and COPD association was used (Fig 4.1).

TABLE 5 Final consensus definition
The association of COPD and bronchiectasis is defined as the presence of at least four elements
1. RADIOLOGICAL: Abnormal bronchial dilatation in one or more pulmonary segment in more than one lobe and specific radiological findings (airways visible within 1 cm of pleura and/or lack of tapering sign) plus
2. OBSTRUCTION: a functional obstructive pattern (post-bronchodilator FEV_1/FVC <0.7), plus
3. SYMPTOMS: two or more of the following symptoms: cough, expectoration, dyspnoea, fatigue, frequent lower airway infections (⩾2/year) plus
4. EXPOSURE: current or past smoking habit (⩾10 pack-years) or other toxic exposure (biomass, industrial, *etc.*)
FEV_1: forced expiratory volume in the 1 s; FVC: forced vital capacity.

Figure 4. 1: ROSE criteria for the diagnosis of BE-COPD. From Traversi et al, ERJOR 2021 (217)

- **CRS** the likelihood of CRS was stratified according to the results of symptoms questionnaire, endoscopy and CT scan, when available (Fig 4.2).

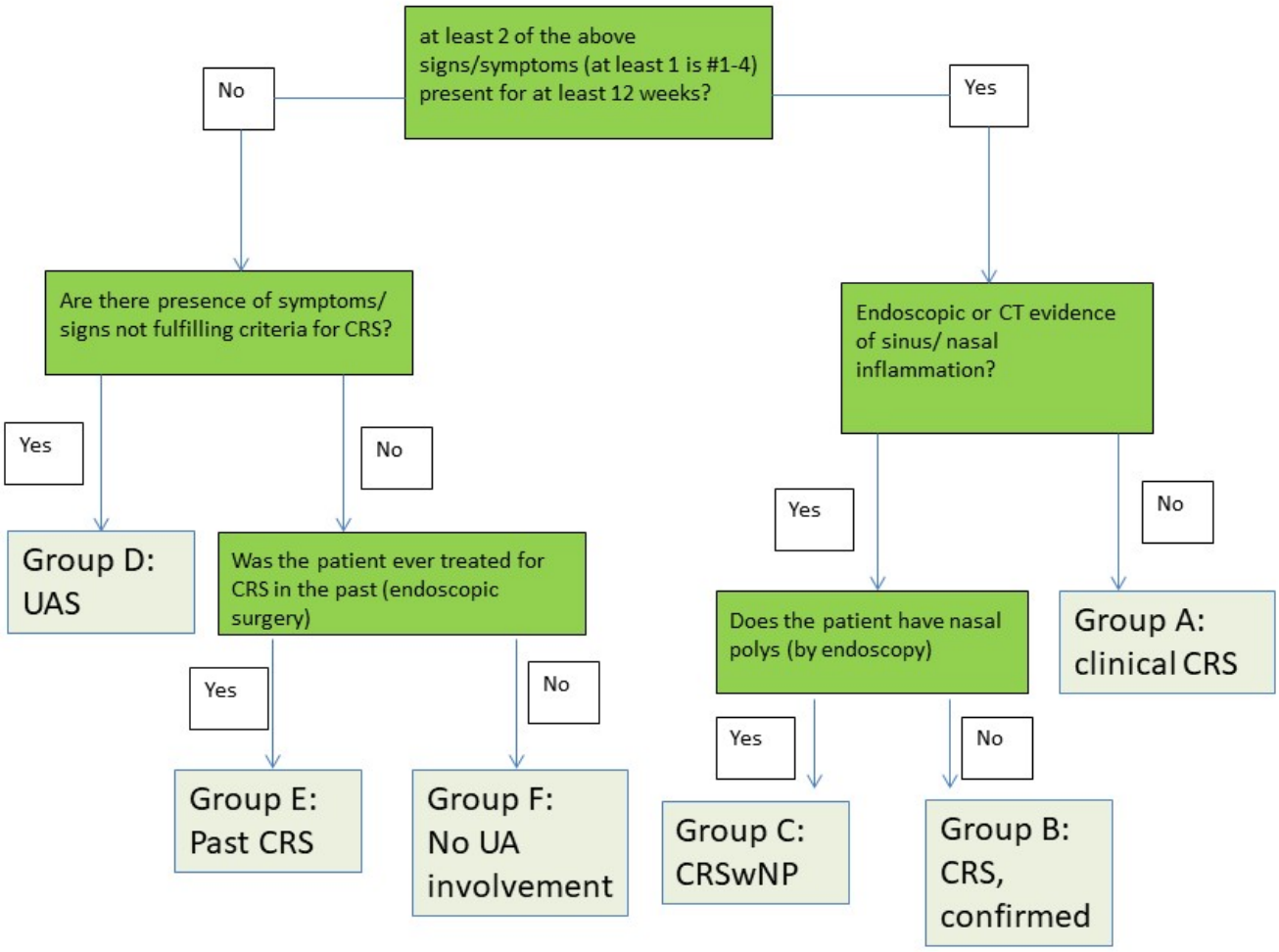


Figure 4.2. Patient stratification according to the likelihood of CRS.

Abbreviations: CRS: Chronic Rhino-Sinusitis; CRSwNP: Chronic Rhino-Sinusitis with Nasal Polyposis; UA: Upper Airway; UAS: Upper Airway Symptoms

5. RESULTS

5.1 DEMOGRAPHIC DESCRIPTION AND BE CHARACTERIZATION

5.1 DESCRIPTION OF THE POPULATION, COMORBIDITIES AND TREATMENT

77 patients were included in the study, 61 (79.0%) females, median age 63 y.o (range 20-82). Almost half of the patients (n:38, 49.3%) had bronchiectasis diagnosed more than 15 years before the enrolment, while only 7 patients (9.1%) had less than 5 years of follow-up.

Osteoporosis was the most prevalent comorbidity (n:16, 21.3%), followed by oesophageal gastric reflux (n:12, 15.6%), depression (n:12, 15.6%) cardiovascular diseases (n:9; 11.8%) and anxiety (n:8, 10.4%). Eight patients (10.4%) had a previous diagnosis of neoplastic diseases, mostly breast cancer (3 patients); none had been diagnosed of lung cancer. while other chronic non respiratory treatment investigated were uncommon, a third of patients received proton pump inhibitor treatment (n: 27, 35.1%). (Tab 5.1)

Two patients died during the year posterior to study visit. In one case, death was correlated with patient's respiratory condition.

Age at consent	
Mean (SD)	58.1 (16.71)
Median (Q1; Q3)	63 (46; 71)
(Min; Max)	(20; 82)
N	77
Gender	
Male	16 (21.0%)
Female	61 (79.0%)
Ethnicity	
White European	74 (97.3%)
Hipanic	1 (1.3%)
Other	1 (1.3%)
How long has the patient had BE?	
< 5 years	7 (9.1%)
5-9 years	13 (16.9%)
10-15 years	19 (24.7%)
15-20 years	11 (14.3%)
20-25 years	12 (15.6%)
> 25 years	14 (18.2%)

Non-respiratory comorbidities	
Osteoporosis	16 (20.8%)
Depression	12 (16.0%)
Cardiovascular disease	9 (12.0%)
Myocardial infarction	2 (22.2%)
Angina	1 (11.1%)
Others	7 (70.0%)
Anxiety	8 (10.4%)
Neoplastic disease	8 (10.4%)
Brest	3 (37.5%)
Haematological	2 (25.0%)
Skin	1 (12.5%)
Lung	1 (12.5%)
Other	1 (12.5%)
Diabetes	2 (2.6%)
Chronic renal failure	1 (1.3%)
Non-respiratory treatment	
Proton-pump inhibitor	27 (35.1%)
Statin	11 (14.3%)
Aspirin	5 (6.5%)
Angiotensin-converting-enzyme inhibitor	4 (5.2%)
Angiotensin II receptor blocker	4 (5.2%)
Beta-Blocker	4 (5.2%)
Warfarin/Oral anticoagulants	2 (2.6%)

Table 5.1: Demographic description of the cohort and comorbidities.

5.1.2 BE CHARACTERIZATION

The most common aetiologies of BE in our cohort were post-infective (n:27, 35.5%) and idiopathic (n:18, 23.4%). (Tab 5.2)

Table 5.2: BE aetiology

Underlying aetiology	n (%)
Post-infective	27 (35.1%)
Idiopathic	18 (23,4%)
Primary ciiary dyskinesia	8 (10.4%)
Kartagener síndrome	*1 (1.3%)*
Primary immunodeficiency	8 (10.4%)
Common variable immunodeficiency (CVID)	*6 (7.8%)*
Hypogammaglobulinemia	*1 (1.3%)*
IgA deficiency	*1 (1.3%)*
Gastroesophageal reflux disease	3 (3.9%)
Connective tissue disease	2 (2.6%)
Aspiration	1 (1.3%)
Inflammatory bowel disease	1 (1.3%)
Post-tuberculous	1 (1.3%)
Rheumatoid arthrits	1 (1.3%)
Other	5 (6.5%)

Severity was assessed using both the FACED and BSI scores. The concordance between the two was significant, both for severity categories (mild, moderate, severe; Cohen's kappa=0.5887, $p < 0.0001$), and for total ordinal scores (Spearman's $\rho = 0.8218$, $p < 0.0001$). (Tab 5.3). According to both classifications, most patients had mild or moderate disease.

Table 5.3: Comparison of BE severity according to Bronchiectasis Severity Index (BSI) and FACED scores.

	BSI			Cohen's Kappa	Spearman correlation
	Mild	Moderate	Severe		
FACED Mild	28	8	0	k=0.5887 p < 0.0001	Rho = 0.8218 p < 0.0001
Moderate	2	18	5		
Severe	0	5	10		

As expected, most patients referred one or more typical BE symptoms (Tab 5.4).

Table 5.4: BE symptoms

Daily sputum volume	**n=76**
Mean (sd)	17.4 (18.2)
Median (Q1; Q3)	10 (5.0; 20)
(Min; Max)	(0; 100)
None/minimal (<5ml/day)	21 (27.6%)
Mild (5-15ml/day)	27 (35.5%
Moderate (15-30ml/day)	13 (17.1%)
Abundant (≥30ml/day)	15 (19.7%)
Sputum colour when stable	**n=76**
Mucoid	19 (25.0%)
Mucopurulent	33 (43.4%)
Purulent	20 (26.3%)
Purulent (severe)	4 (5.3%)
mMRC dyspnea scale	**n=77**
0	41 (53.2%)
1	30 (39.0%)
2	3 (3.9%)
3	3 (3.9%)
4	0 (0%)
Respiratory exacerbations during last 12 months	n=77
Mean (SD)	1.27 (1.82)
Median (Q1; Q3)	1 (0; 1)
(Min; Max)	(0; 11)

While 21 patients (27.6%) reported absent or minimal daily expectoration, sputum production in the remaining patients varied. Mild expectoration (5–15 ml/day) was reported by 27 patients (35.5%), while moderate (15–30 ml/day) by 13 patients (17.1%), whereas high expectoration (≥30 ml/day) was reported by 15 patients (19.7%).

Expectoration was mostly mucopurulent (n:33, 43.4%) or purulent (n:19, 26.3%); only 4 patients (5.3%) reported stable severe purulent expectoration. Mucous sputum was referred by 19 subjects (25.0%), most of them reporting minimal sputum production.

More than half of the patients did not experience dyspnoea in their daily life (n:41, 53.2%). Mild dyspnoea (mMRC 1) was present in 30 patients (39.0%), while moderate and severe dyspnoea (mMRC 2-3) were reported by 3 patients (3.9%) each. None referred resting dyspnoea.

Cough in stable state was experienced by most patients in more than 50% of the days (n:31, 41.3%) or occasionally (n:37, 49.3%). Only 7 patients had no cough when stable (9.5%).

Sixty-six patients completed the Leicester Cough Questionnaire (LCQ) questionnaire, with mean total score of 15.3 (SD 3.84). Final scores allocated 26 patients (39.4%) in the Mild group, 25 (37.9%) in “moderate” category and 15 (22.7%) in “Severe”. (Tab 5.5)

Table 5.5: Cough assessment

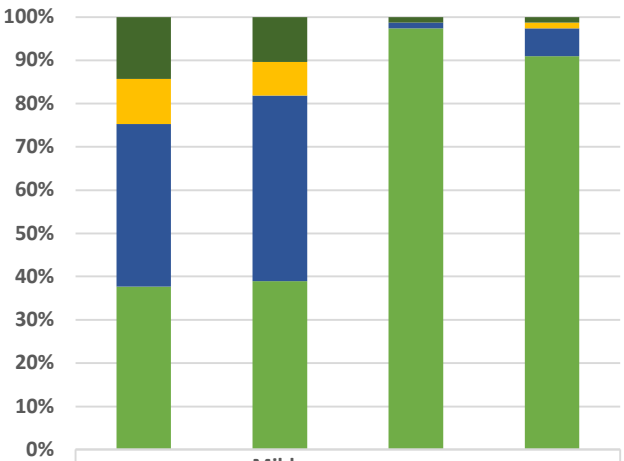
Leichester cough questionnaire results expressed as mean scores (SD)			
Physical domain	5.12 (110)		
Psychological domain	5.02 (1,57)		
Social domain	5.22 (1,40)		
TOTAL	15.3 (3,84)		
Severity according to Total LCQ score:	**Mild (17,54 – 21,00)**	**Moderate (12,29-17,53**	**Severe (3.00-12.28)**
	26 (39.4%)	25 (37.9%)	15 (22.7%)
Cough frequency	**Almost never**	**Occasional (20-50% of the time)**	**Frequent (≥50% of the time)**
Self-reported cough frequency	7 (9.5%)	37 (49.3%)	31 (41.3%)
Mean LQR score according to cough frequency:	19.9 (0.88)	16.6 (3.02)	12.7 (3.25)

As expected, all patients that referred infrequent cough had higher scores (mean 19.9, SD 0.88) indicating minimal or absent impact of the symptom on their lives, while the lower scores belonged to the group that reported habitual cough (mean 12.7, SD 3.25).

When considering each domain separately, their mean values appear very similar: physical domain mean score was 5.12 (SD 1.10), psychological 5.02 (SD 1.10), and social impact 5.22 (SD 1.40). Mean and median values of individual items are similar across most questions. However, lower values, indicating a greater impact, were observed for the question about lack of energy.

LCQ scores had significant correlation with ACT, CAT and SGQR ($p<0.001$).

Regarding acute episodes, 29 patients (37.7%) had no exacerbations in the year before enrolment, 29 (37.7%) had one exacerbation, 8 (10.4%) had two exacerbations and 11 (14,3%) had three or more exacerbations per year. Only 2 subjects (2.6%) had one or more hospital admissions, while 7 patients (9.1%) consulted the Hospital Emergency Department and were discharged with home treatment (Fig. 5.1).



	Overall	Mild-Moderate	Severe*	ED visits**
≥3	14%	10%	1%	1,30%
2	10%	8%	0%	1,30%
1	38%	43%	1%	6,60%
0	38%	39%	97%	92,10%

Figure 5 1: frequency and severity of exacerbations. *Note: *: severe exacerbations defined as requiring IV treatment and/or hospitalization; ** not resulting in hospitalization. ED=Emergency Department*

5.1.3 RESPIRATORY TREATMENT

Most patients (n: 66, 85.7%) were receiving at least one chronic respiratory treatment at their first visit, with inhaled therapies being the most common (n: 56, 72.7%): LAMA were prescribed to 19 patients (24.7%), ICS/LABA to 42 (54.5%), LABA/LAMA combination to 7 (9.1%), while only one patient received triple bronchodilator treatment. Additionally, 10 patients (13.0%) were treated with short-acting nebulized bronchodilators.

Immunoglobulin replacement therapy was administered to 7 patients (10.7%), either via intravenous (n:5, 71.4%) or subcutaneous route (n:2, 28.6%).

Chronic antibiotic use was common: 18 patients (23.4%) reported using nebulized antibiotics, being colistin in 17 and ampicillin in 1. On the other hand, 32 subjects (41.6%) were receiving chronic oral antibiotic, mostly azithromycin 3 days/week (n: 28, 87.5% of chronic ATB users) (Tab 5.6).

Physiotherapy was reported by only 31 patients (40.3%). However, actual adherence to the treatment could not be assessed. All these patients had previously attended Pulmonary Rehabilitation to receive instruction in drainage techniques. In contrast, for 38 patients (52.8%), physiotherapy was not considered necessary by either the patient or the clinician. A small number of patients were not referred due to comorbidities (n: 1) or failed to attend

the program (n: 2). Autonomous drainage, directed ventilations, and Expiration Lente Totale Glotte Ouverte en décubitus Latéral (ELTGOL) were the most commonly used techniques, while Acapella was the most frequently utilized device.

Only 9 patients (11.7% of the cohort) were using nebulized hypertonic saline, 3 of them with sodium hyaluronate (HYANEB©).

Table 5.6: Pharmacological and Non-Pharmacological Therapies

Respiratory treatments	**n (%)**
Patients receiving regular respiratory treatment	66 (85.7%)
ICS/LABA	42 (54.5%)
LAMA	19 (24.7%)
LAMA/LABA	7 (9.1%)
ICS/LAMA/LABA	1 (1.2%)
Nebulised bronchodilators	10 (13.0%)
Intravenous/subcutaneous immunoglobulins	7 (10.7%)
Antimicrobial treatment	
Inhaled Nebulised antibiotics	18 (23.4%)
Long term antibiotics	32 (41.6%)
of which azithromycin	28 (87.5%)
Antifungal	1 (1.2%)
Physiotherapy and physiotherapy adjuncts	
Regular physiotherapy	31 (40.3%)
Nebulised Hypertonic saline	9 (11.7%)
of which sodium hyaluronate	3 (33.3%)
Attended Pulmonary Rehabilitation	31 (40.3%)
Not referred PR (considered not necessary)	38 (52.8%)
Did not attend PR (comorbidities/no adherence)	3 (3.9%)

Legend: ICS: Inhaled Corticosteroid; LABA: Long-Acting Beta-Agonist; LAMA: Long-Acting Muscarinic Antagonist; PR: Pulmonary Rehabilitation

5.2 ASTHMA, COPD AND CRS: CLINICAL EVALUATION

5.2.1 ASTHMA SYMPTOMS

Patients underwent a standardized interview to assess asthma-like signs and symptoms, based on clinical features outlined in the GINA guidelines as indicative of the disease. Questions evaluated the presence of the symptoms at any time in patients' life, their variability, and possible correlation with infection or other external factors.

As expected, cough was the most frequently reported symptom, cited by 61 participants (80.3%). Surprisingly, wheezing, a symptom less commonly associated with BE, was present in more than half of the cohort (n: 45, 59.2%). Shortness of breath and chest tightness were reported by nearly a third of patients, while only a small portion of the sample had never experienced any of these symptoms (n:8, 10.5%).

In most cases, symptoms appeared or worsened during infections (n: 43, 63.2%). Additionally, 37 subjects (54.4%) noted that symptom severity varied over time. Among ever-symptomatic patients, nearly half reported that symptoms were triggered by exercise, laughter, allergens, or cold temperatures, while an equal proportion described worsening symptoms at night or upon waking (n:28, 41.2% for both).

To further investigate asthma-related symptoms, patients were asked about wheezing frequency in the month before their visit. While most had not experienced wheezing (n:40, 57.1%), 17patients (24.3%) reported occasional episodes, 4 had frequent occurrences (5.7%), and 3 (4.3%) experienced it almost daily.

Family history of asthma was reported by 40.5% of patients (n: 31), affecting parents, siblings, and descendants equally.

Aspirin allergy or intolerance was reported by only 2 patients.

More than half of the cohort (n: 44, 57.9%) did not report daily exposure to inhalants. Pets were the most common source (n: 21, 27.6%). Workplace exposure to hazardous dust (n: 8, 10.4%) and second-hand smoke (n: 3, 3.9%) was observed in a smaller number of patients. No association was evidenced between exposures and symptoms appearance (Tab 5.7).

Table 5.7: Assessment of asthma symptoms

Reported asthma symptoms at any time in life	**n (%)**
Wheeze	45 (59.2%)
Shortness of breath	30 (39.5%)
Chest tightness	26 (34.2%)
Cough	61 (80.3%)
None	8 (10.5%)
Variability of symptoms	
Occur variably over time and vary in intensity	37 (54.4%)
Are often worse at night or on waking	28 (41.2%)
Are often triggered by exercise	28 (41.2%)
Often appear or worsen with viral infections	43 (63.2%)
Is there any member of your family with known history of asthma?	
No	46 (60.5%)
Yes	31 (40.5%)
Siblings	7 (9.21%)
Descendants	6 (7.89%)
Mother	5 (6.58%)
Father	4 (5.26%)
Sons	3 (3.95%)
Other	3 (3.95%)
Unknown	2 (2.63%)
Aspirin intolerance/aspirin-related asthma	
Yes	2 (2.63%)
No	72 (94.74%)
Unknown/No answer	2 (2.63%)
Frequent/daily exposure to inhalants	
Hazardous dusts	8 (10.53%)
No	44 (57.89%)
Secondhand smoke	3 (3.95%)
Pets	21 (27.63%)

5.2.2 COPD INVESTIGATION: SMOKING AND OTHER EXPOSURES

Table 5.8: History of noxious exposures

Variable	N (%)
Never smoker	59 (76.6%)
Current smoker	2 (2.6%)
Ex smoker	16 (20.8%)
Approximate Pack-Year	
0-4	6 (37.5%)
5-9	2 (12.5%)
10-20	4 (25.0%)
21-40	3 (18.8%)
>41	1 (6.3%)
Significant noxious exposure	6 (7.8%)

Considering that COPD symptoms, such as cough and dyspnoea, are non-specific and have already been reported in previous sections, we did not include a separate analysis of COPD symptoms.

A history of tobacco consumption was reported by 18 patients (20.8%), including 16 ex-smokers and 2 active smokers. Half (n: 9, 10.4%) had a cumulative consumption of less than 10 pack-years, while the other half had 10 or more pack-years.

Only six patients (7.8%) had a history of prolonged occupational or environmental exposure potentially linked to the development of chronic respiratory diseases.

History of exposures is detailed in Tab 5.8.

5.2.3 CHRONIC RHINOSINUSITIS SYMPTOMS

When administered the signs and symptoms questionnaire, 29 patients referred the presence of at least one upper airway symptom (UAS) (39.7%); 20 patients (28.8%) presented two or more symptoms for at least 12 weeks.

Nasal congestion, obstruction and blockage were the most common symptoms (respectively 20.5%, 19.2% and 17.8% of responders). Facial pain, on the other hand, was only seldomly reported (n: 5, 6.8%). Fourteen symptomatic patients (66.6%) underwent sinonasal endoscopy or facial CT, confirming sinonasal inflammation in 9 cases (42.8%), with nasal polyps detected in 4 (28.6%) of them (Table 5.9).

Regarding asymptomatic patients, three had previously undergone sinonasal surgery and had remained symptom-free thereafter.

Table 5.9 Evaluation of clinical symptoms of CRS

Symptom experienced	No	Yes, < 12 weeks	Yes, > 12 weeks
Nasal blockage	50 (68.5%)	10 (13.7%)	13 (17.8%)
Nasal obstruction	49 (67.1%)	10 (13.7%)	14 (19.2%)
Nasal congestion	44 (60.3%)	14 (19.2%)	15 (20.5%)
Nasal discharge	51 (69.9%)	12 (16.4%)	10 (13.7%)
Facial pain or pressure	63 (86.3%)	5 (6.8%)	5 (6.8%)
Reduction or loss of smell	58 (79.5%)	4 (5.5%)	11 (15.1%)
At least 1 upper airway symptom			29 (39.7%)
At least 2 symptoms for > 12 weeks			20 (27.4%)

5.3 QUALITY OF LIFE ASSESSMENT

5.3.1 SAINT GEORGE RESPIRATORY QUESTIONNAIRE

A total of 67 patients completed the SGRQ. The mean score for the entire cohort was 40.9 (SD 16.5; median 40.7). While activity and impact scores were comparable, the symptoms domain showed slightly higher mean values (46.4, SD 20.13; median 49.1).

Since the SGRQ lacks validated severity thresholds, we arbitrarily categorized the scores into four groups: 0–25, 25.01–50, 50.01–75, and 75.01–100. (Table 5.10). Most patients (n = 28, 41.8%) scored between 50 and 75 in the symptoms' domain, indicating a notable symptomatic burden. However, daily activities and psychosocial well-being appeared to be only moderately affected, as 67.2% and 71.6% of patients, respectively, scored below 50 in these two domains. Women scored significantly higher than men in the 'Impact' domain, but not in the other domains (p=0.0057).

Table 5.10 Summary of Saint George Respiratory Questionnaire results

Domain	Mean	Median
Symptoms	46.4 (20.13)	49.1 (30.7; 60.35)
Activity	39.12 (24.76)	41.72 (18.47; 58)
Impact	40.5 (15.6)	40 (28.6; 52.8)
Total	40.9 (16.5)	40.7 (20.0; 51.22)
Categories (quartiles)		
0-25		12 (17.9 %)
25.01-50		34 (50.7 %)
50.01-75		18 (26.9 %)
75.01-100		3 (4.5 %)

SGRQ quartiles, but not the numerical scores, showed a significant correlation with the number of mild and moderate exacerbations ($p<0.05$). Regarding FEV_1, we observed that only absolute values (litres), and not percent predicted values, correlated significantly with

SGRQ scores ($p<0.05$ for both numerical scores and quartiles). Dyspnoea defined by mMRC scores also correlated with SGRQ scores and quartile categorization (respectively $p<0.005$ and $p<0.05$). No correlations were found with other variables, including aetiology, disease severity, sputum volume or CBI status (for any PPM or PA), but SGRQ total scores correlated with ACT, CAT, LCQ and SNOT-22 (all $p<0.001$)

5.3.2 ASTHMA CONTROL TEST

Patients were instructed to answer the ACT questions based on the presence of symptoms such as wheezing, chest tightness, and sudden shortness of breath, instead of using the term 'asthma'.

Table 5.11 Summary of Asthma Control Test results

	N=66
Mean (SD)	21.11 (3.88)
Median (Q1;Q3)	22 (19; 24)
Categories	
Well controlled n (%)	48 (71.6%)
Poorly controlled n (%)	8 (11.9%)
Not well controlled n (%)	11 (16.4%)

While most patients that completed the ACT reported good control of wheezing and chest tightness (n: 48, 71.6%), poor control was reported by 8 (11.9%) (Tab.5.11). Mean scores did not show great variabilities between different questions, but lower scores (1, 2) were more frequent in questions regarding morning symptoms and rescue inhaler use.

ACT did not show any correlation with significant variables, such as exacerbations, lung function, chronic infection, nor with severity expressed with BSI and FACED scores. However, scores had significant correlation with all the other QoL tests (CAT, SGRQ, LCQ and SNOT-22, all $p<0.001$).

5.3.3 COPD ASSESSMENT TEST

Only 53 patients completed the CAT. Mean score was 15.8 (SD 7.53, median 16), indicating a predominance of moderate symptoms. Only 12 patients totalized high or very high scores (Tab 5.12)

The analysis of single questions revealed that cough, expectoration and exertional dyspnoea are the most impactful symptoms in our cohort, as stressed out by higher frequencies of answers ≥3 points (respectively 35 patients, 66.0%; n: 29, 54.7%; n: 30, 56.6%).

CAT scores showed a significant negative correlation with absolute FEV1 values, but not with FEV1 percent predicted nor with the degree of airflow obstruction as defined by the FEV1/FVC ratio. Similarly, no association was observed with severity scores (BSI and FACED).

Table 5.12 Summary of COPD Assessment Test results

	N=52
Mean (SD)	15.76 (7.48)
Median (Q1;Q3)	16 (9.5; 19.75)
Categories	
Low n (%)	14 (26.9%)
Medium n (%)	26 (50.0%)
High n (%)	10 (19.2 %)
Very High n (%)	2 (3.8%)

Significant association was also observed between CAT categories and exacerbation frequency. (p<0,05), and between CAT numerical scores and dyspnoea (p<0.05).

Moreover, CAT results had good correlation with the other tests: SGRQ, ACT, and SNOT-22 (all p<0.001)

5.3.4 SNOT-22

The effect of CRS symptoms was evaluated using the SNOT-22 questionnaire in 66 participants (Tab 5.13).

While 25 patients (37.9%) reported absent or mild upper airways symptoms, the majority experienced a moderate impact from sinonasal symptoms (n: 30, 45.5%). In 11 patients (16.7%) these symptoms had a severe impact. Dividing the questions according to the specific domain considered(239), the burden of rhinological symptoms seems to be slightly higher, while ear and facial symptoms obtained the lower scores (Tab 5.13). Noticeably, significant differences were recorded between male and female subject: overall score, psychological dysfunction and sleep dysfunction were significantly higher in females (respectively p=0.016, p=0.007 and p=0.002).

SNOT-22 results did not show association with BE severity scores, but were correlated with LCQ, CAT and SGRQ questionnaires (all p<0.001).

Table 5.13 Summary of Sinonasal Outcome Test

Domain (score range)	Mean (SD)	Median (Q1; Q3)
Overall score	34.47 (19.82)	30 (17; 44)
Rhinologycal symptoms (0-30)	8.88 (6.96)	8 (3; 14
Extranasal symptoms (0-15)	5.64 (3.27)	5 (3: 8)
Ear/facial symptoms (0-25)	4.20 (4.39)	3 (1.25; 5)

Psychological dysfunction (0-35)	10.76 (8.70)	8.5 (3; 18)
Sleep dysfunction (0-25)	8.39 (6.64)	7 (3; 14)

5.4 FUNCTIONAL ASSESSMENT

All patients underwent spirometry, while PBD was realized in 76 patients (Tab 5.14); in 3 cases, PBD was not realized during the study, but data from the 12 months prior were utilized. These data had been collected by our team during a previous study, allowing us to guarantee for technical rigour and uniformity of instruments and technique.

Plethysmography was performed in 63 patients (81.8%), while DLCO in 58 (75,3%).

Considering the whole cohort, mean post-bronchodilator FEV1 was 81.1%, mean FVC 86.9%.

Table 5.14. Summary of main pulmonary function parameters

Variable	Mean (SD)	Median (IQR)	N
FVC L post-BD	3.0 (0.96)	2.91 (2.13; 3.58)	75
FVC% post-BD	85.9 (19.9)	88.9 (74.9; 97.5)	75
FEV1 L post-BD	2.2 (0.76)	2.2 (1.52; 2.52)	75
FEV1% post-BD	81.1 (20.3)	79.7 (67.7; 95.6)	75
FEV1/FVC% post	74.6 (9.8)	75.6 (68.5; 80.6)	75
TLC%	91.4 (18.4)	92.4 (80.3; 101.4)	63
DLCO%	76.3 (13.6)	75.2 (68.1; 88.1)	58
DLCO/VA%	98.2 (14.0)	100.3 (87.3; 108.0)	58
RV%	110.4 (36.1)	109.7 (85.4; 134.3)	63

Abbreviations: FVC: Forced Vital Capacity; FEV1: Forced Expiratory Volume in 1 second; FEV1/FVC: Ratio between FEV1 and FVC; TLC: Total Lung Capacity; DLCO/VA: Diffusing Capacity of the Lung for Carbon Monoxide corrected for Alveolar Volume; SD: Standard Deviation; IQR: Interquartile Range; N: Number of subjects.

At least one lung function test (LFT) alteration was present in most patients (53/77, 68.8%), being the most common obstruction.

Thirty-five patients had a normal spirometry (45.5%); among them, only 16/58 (27% of those that realized all LFT, 20.8% of the entire cohort) also had normal lung volumes and transfer coefficient for carbon monoxide (KCO).

Obstructive pattern was the most common functional impairment (n:21, 27.6%); in 13 subjects air trapping was also present (16.9% of the cohort, 61.9% of patients with obstruction) together with DLCO impairment in 8 (13.8% of the cohort, 50.0% of patients with obstruction).

Air trapping without obstruction was present in 12 more patients (19.0% of subjects with plethysmography, 15.6% of the cohort).

On the other hand, 8 subjects (12.7%) presented with a restrictive pattern; in 3 more, forced spirometry was indicative of possible restriction, that was not confirmed due unavailability of plethysmography. Between restricted or possibly restricted patients, 7 had DLCO impairment and three presented air trapping.

Overall, air trapping was observed in 25 out of 63 patients (39.7%).Mixed functional pattern was present in 2 patients (3.2%).

DLCO impairment without any other alteration was manifest in 12 patients (20.7%).

Notably, although DLCO values were reduced in most patients (35/58, 60.3%), only a small proportion (6/58, 10.3%) showed reduced values when corrected for alveolar volume (DLCO/VA). Distribution of different LFT pattern is resumed in Fig 5.2.

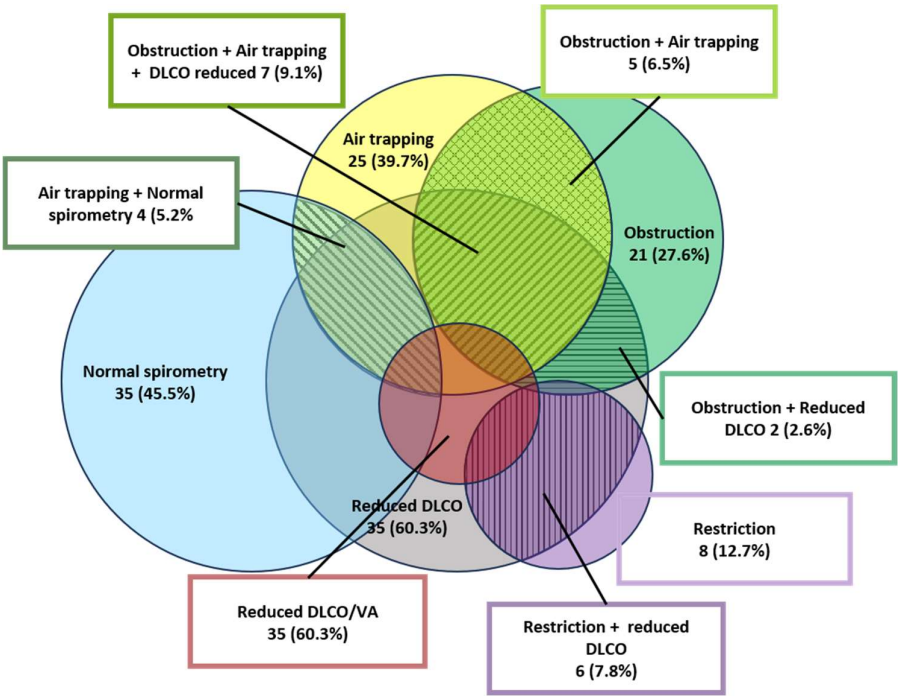


Figure 5.2 Distribution of alterations in lung function.

Abbreviations: DLCO: Diffusing Capacity of the Lung for Carbon, DLCO/VA: Diffusing Capacity of the Lung for Carbon Monoxide corrected for Alveolar Volume

Surprisingly, only 4/76 patients presented reversibility at the PBD test, 3 females and one male. While post BD FEV1 values were comparable with the entire cohort (mean 84.7%, median 80.6%, SD 13.3), pre-BD values were significantly lower (mean 70.7%, median 63.9%, SD 18). The mean FEV1 change was 12% of the predicted value.

Three out of the four patients exhibited a FEV1/FVC ratio >70%; the fourth patient had an obstructive pattern both before and after the BD administration. Two subjects had air trapping and one diffusion impairment.

In 49 patients, six months spirometry follow up was available. Comparing FEV1 values from the year prior to enrolment with those six months after, we observed no significant variation in post-BD FEV1. The mean absolute change in FEV1 was -0.12 L (SD 0.54, p=0.13), and the mean percentage change was -2.35% (SD 12.79, p=0.20). Only 8 subjects (10.4%) exhibited significant variability (>20%) over time.

5.5 INFLAMMATION AND ALLERGY

Despite all the samples were collected in stable state, a few patients showed mild alterations possibly indicative of chronic inflammatory state: 10 patients (13%) presented slightly elevated white cell count (mean 11.5×10³/μL, SD 1,37), while 18 (23,38%) had C reactive protein levels above 0.5 mg/l (mean 1.08 mg/l, SD 0.506). Only 3 patients exhibited both alterations.

No correlation was observed between higher levels of white blood cells or CRP and the presence of chronic infection, purulent sputum production or other inflammatory markers (eosinophils, IgE, Phadiatop, FeNO).

Peripheral eosinophilia (eosinophils > than 300/mm^3) was present in 12 patients (15.6%), mean value 0.533×10³/μL, median 0.500×10³/μL, SD 0.172). In all of them specific causes of eosinophilia were discarded.

On the other hand, neutrophilia was evident in 7 patients (9.1%; mean value 9.26×10³/μL, median 8.90×10³/μL, SD 1.154).

The presence of eosinophilia was correlated with lesser sputum purulence and reduced prevalence of PA CBI (both $p<0.05$). Moreover, correlation was observed with FeNO levels ($p<0.005$) and IgE count ($p=0.005$).

Contrarily, patients with blood neutrophilia did not show any significant correlation with other clinical or functional and radiological variables.

On the other hand, lung function showed no significant correlation with peripheral eosinophil or neutrophil counts.

FeNO levels were recorded in 74 patients. Nineteen of them (25.7%) had values >25ppb (mean 42.2, median 37, SD 15.5). FeNO levels showed inverse correlation with the number

of lobes affected by BE. Apart from this and eosinophil counts, FeNO was not significantly correlated with any other clinical or inflammatory variables.

IgE count was <150 µL in 86.3% of the cohort (n:63); 5 patients (7,94%) had IgE between 150 and 300, 4 patients had values between 300 and 1000, while only one patient presented severe hyperIgE. In this last patient, ABPA was ruled out and revision of medical records confirmed sustained hyperIgE without recognizable cause. Levels of IgE showed a positive correlation with higher eosinophil count, but not with FeNO.

Phadiatop was positive in 14 of the 72 patients tested (19.44%) with 5 of them showing elevated IgE levels.

Other blood test results and FeNO are resumed in Table 5.15.

Table 5.15: Descriptive statistics and distribution of inflammatory markers

Variable	Mean	Median	N
White Blood Cells 10^3/µL	7.35 (2.2)	7.1 (5.7; 8.3))	73
Blood neutrophils %	59.3 (10.7)	59.9 (52.1;65.6)	73
Blood eosinophils %	2.6 (2.3)	1.7 (1.0;3.2)	73
Blood neutrophils 10^3/µL	4.5 (2.0)	4.1 (3.0;5.0)	73
Blood eosinophils 10^3/µL	0.2 (0.2)	0.1 (0.1;0.2)	73
C-reactive protein mg/L	0.4 (0.5)	0.4 (0.0;0.5)	72
FeNO ppb	20.8 (15.6)	16.5 (10.0;25.8)	74
FeNO > 25 ppb	19 (25.7%)		
Immunoglobulin E kU/L	104.8 (281.9)	22.8 (11.3;81.0)	73
IgE <150 µL kU/L **IgE 150 – 300 kU/L** **IgE 300 – 1000 kU/L** **IgE >1000 kU/L**	63 (86.3%) 5 (7,9%) 4 (5.4%) 1 (1.3%)		
Phadiatop positive, n (%)	14 (19.44)		72

5.6 MICROBIOLOGY ASSESSMENT:

At least one sputum sample was collected during visit one or in the previous 12 months (in a clinically stable state) in 51 patients (66.2%). Among them, only 3 (5.9%) had no microorganism isolation. In the remaining 48, a total of 73 microorganisms were isolated (Tab 5.16).

Table 5.16: Summary of microbiology key findings

Variable	N (%)
Clinically stable samples last 12 months	51 (66.2%)
Organism isolated	48 (94.1%)
Pseudomonas aeruginosa	20 (39.2%)
Streptococcus pneumoniae	4 (8.3%)
Aspergillus spp	6 (11.8%)
Stenotrophomonas maltophilia	6 (11.8%)
Staphylococcus aureus	7 (13.7%)
Haemophilus influenzae	8 (15.7%)
Candida sp.	9 (18.7%)
Chronic Bronchial Infection	44 (58.6%)
CBI for PA	31 (43.1%)
CBI for other PPM	29 (38.6%)

Abbreviation: CBI: chronic bronchial infection; PA: Pseudomonas aeruginosa; PPM: potentially pathogenical microorganism

PA was the most common bacterial isolate, detected in 20 of 51 sputum samples (39.2%), followed by *H. influenzae* (n: 8, 15.7%), *S. aureus* (n: 7, 13.7%), and *S. maltophilia* (n: 6, 11.8%). Fungi were also frequently isolated: *Candida* spp. was found in 9 patients, and *Aspergillus* in 6 (11.8%; 5 *A. fumigatus*, 1 *A. niger*). Only one sputum culture was positive for mycobacteria, showing growth of *M. abscessus* colonies; however, the patient did not fulfil criteria for NTM-PD.

Data on previous isolations and known CBI were available for 75 patients, with CBI diagnosed in 44 (58.6%). *PA* was responsible for CBI in 31 patients (43.1%), including 18 with current *PA* positive sputum. In 6 patients (19.3%), *PA* had not been isolated in the past 5 years, while in 7 others (22.6%), the last isolation occurred more than 24 months before study inclusion. However, all these patients were considered to have active *PA*-CBI, as previous attempt of eradication had failed and they were receiving ongoing chronic inhaled *PA* treatment that could interfere with culture results. *PA* chronic infection had been present, on average, for 8 years and 2 months (mean 8.21 years, median 7.6 years, SD 6.55). In 13 cases, chronic *PA* infection (43.3%) was sustained by mucoid phenotype of the bacteria.

Apart from *PA*, other pathogens were responsible for CBI in 29 subjects, being the most frequent *H. influenza* in 11 patients (37,9%) and *S. aureus* in 7 (24,1%). Patients had been presenting CBI for 4 years and 10 months on average (mean 4.84; median 4.08 years, SD 4,21). Sixteen patients (21.3%) presented 2 or more concomitant CBIs.

No correlation was observed between the presence of CBI for PA or other PPM and other tested variables.

5.7 RADIOLOGICAL CHARACTERIZATION

Chest HRCT from 76 patients were analysed, while for the remaining patient it was not possible to retrieve the images of the most recent CT. Additionally, expiratory scans were available for 61 patients (80.3%). Results are detailed in Tab 5.17.

According to Reiff modified score, most patients (n: 48, 63.2%) had mild bronchiectasis (Reiff 1-6); moderate radiological extension of BE was recorded in 26 patients (34.7%, Reiff 7-12), while only 2 subjects (2.7%) had severe CT involvement (Reiff ≥13 points).

Table 5.17: Bronchiectasis extension in the cohort

Radiological Finding	N=76
N. of lobes with BE, mean (SD)	3.95 (1.75)
N. of lobes with BE, median (IQR)	4 (3; 6)
Reiff index, mean (SD)	5.71 (3.4%)
Reiff index, median (IQR)	5 (3; 8%)
Reiff Mild (1-6), n (%)	47 (62.67%)
Moderate (7-12), n (%)	26 (34.67%)
Severe (13-18), n (%)	2 (2.67%)
Cystic bronchiectasis, n (%)	15 (19.5%)

We observed a significant negative correlation between Reiff scores and several respiratory parameters: post-BD FVC in litres (ρ=–0.283, p=0.014), post-BD FEV1 (ρ=–0.350, p=0.002), and FeNO levels (ρ=–0.287, p=0.014). When Reiff categories were analysed instead of continuous scores, greater bronchiectasis severity was significantly associated with lower post-BD FVC percentages (p=0.007), lower post-BD FEV1 percentages (p=0.007), and TLC values (p=0.047). Reiff values also showed strong correlation with BSI and FACED scores (both p<0.001).

The extension of BE (Fig.5.3) followed a mild gradient, with significantly higher prevalence in the lower and middle pulmonary lobes compared with upper lobes (p<0.001 for both comparisons). Lower lobes exhibited the highest involvement, as more than 90% of patients presented BE at this level (n: 69, 90.7%), though the difference with middle lobes was not significant (p=0.593). Left lower lobe was the most frequently affected, as only 14 patients (18.4%)

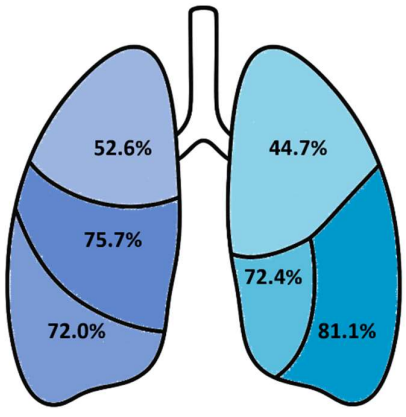


Figure 5. 3 Bronchiectasis lobar distribution. *The percentages indicate the prevalence of bronchiectasis in each lobe.*

did not show bronchial dilatation in this segment. Also, it was the lobe with highest occurrence of cystic BE (7 subjects, 9.2%).

Middle lobe and lingula presented BE in 86% of cases (n: 66), while superior lobes involvement was evident in 64.5% of patients (n: 49).

No differences were found between left and right lobes.

The number of lobes affected by bronchiectasis was inversely correlated with FeNO levels (ρ= –0.290, p=0.013) and FVC values (ρ= –0.327, p=0.004).

Cystic BE were present in 15 subjects (19.7%),

Emphysema was a rare finding, observed in only 2 patients (2.6%).

Most patients had evidence of BWT (n=66, 85.7%), while air trapping was reported in 54 patients, accounting for 88% of those with an expiratory scan available and 70% of the cohort.

The presence of *BWT* and *air trapping* correlated with lower post-BD FEV1 and obstructive pattern. Mean FEV1 was 78.1% vs 96.7 for BWT (p = 0.015), and 79.9% vs 100.0% for air trapping (p = 0.003). FEV1/FVC was lower in patients with BWT (73.0% vs 84.6%, p=0.002) and with air trapping (74.44% vs 79.9%, p=0.025).
BWT also correlated with Reiff index (mean score 6.05±3.29 vs 3.78±3.52, p=0.029), but not with other markers of radiological BE extension.

MP were evident in 52 patients (67.5%), and their presence was associated with more extensive disease. In fact, Reiff scores were higher in patients with MP (mean 6.87 ± 3.24 vs 3.3 ± 2.2, <0.0001), as was the number of affected lobes (median 5 vs 3, p=0.001); cystic bronchiectasis was more frequent (93.33% vs 62.33%, p=0.052). MP also correlated with more the presence of obstructive pattern (mean FEV1 72,2% vs 88.6%, p=0.008; FEV1/FVC 72,2% vs 79.6%, p=0.002).

GGO was observed in 33 scans (43.4%), with a centrilobular pattern suggestive of infection in 21 cases (63.6% of those with GGO). The presence of GGO was associated with higher Reiff scores (median 6.5 vs 4 p<0.001), more numbers of lobes with BE (median 5 vs 3, p<0.001), presence of cystic BE (73.3% vs 37.7, p=0.019) and BWT (50% vs 11.1%, p=0.035).

Results are summarized in fig. 5.4 and Tab 5.18.

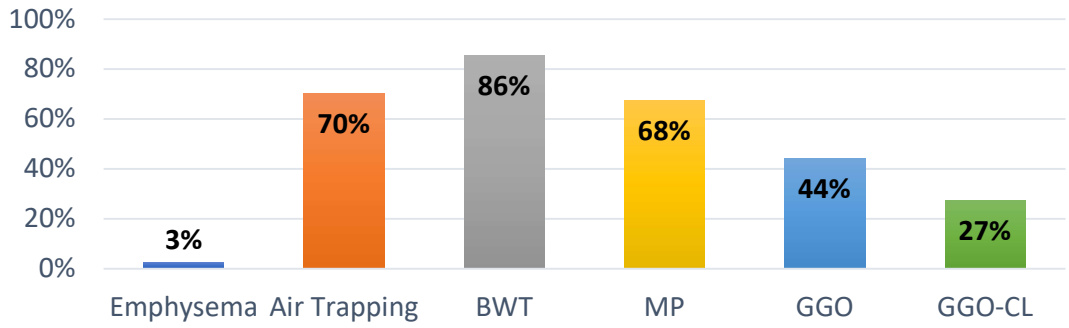


Figure 5. 4 distribution of radiological findings.
Abbreviations: BWT: bronchial wall thickening, MP: mucus plugging, GGO: ground glass opacities; GGO-CL: centrilobular GGO pattern.

Table 5.18: Significant differences according to radiological features.

Bronchial wall thickening	**Present**	**Absent**	**P value**
FEV1 %, mean (SD)	78.1 (18.35)	96.73 (25.87)	0.015
FEV1/FVC%, mean (SD)	73.03 (9.12)	84.56 (9.64)	0.002
Reiff index, mean (SD)	6.05 (3.29)	3.78 (3.53)	0.030
Number of lobes with BE, mean (SD)	4.14 (1.65)	2.89 (1.96)	0.058
Air trapping	**Present**	**Absent**	**P value**
FEV1 %, mean (SD)	79.92 (19.79)	100.01 (9.13)	0.003
FEV1/FVC%, mean (SD)	73.55 (9.4)	81.14 (2.38)	0.026
Mucus plugging	**Present**	**Absent**	**P value**
FEV1 %, mean (SD)	76.84 (19.57)	88.62 (19.53)	0.009
FEV1/FVC%, mean (SD)	72.23 (8.74)	79.6 (10.64)	0.002
Reiff index, mean (SD)	6.87 (3.24)	3.3 (2.2)	<0.001
Number of lobes with BE, mean (SD)	4.42 (1.56)	3 (1.71)	0.001
GGO	**Present**	**Absent**	**P value**
Cystic BE, n (%)	14 (93.3%)	22 (36.7%)	0.052
Reiff index, mean (SD)	7.41 (3.23)	4.33 (2.84)	<0.001
Presence of BWT n (%)	51 (85%)	9 (15%)	0.248

Only significant correlations have been reported in the table.
Abbreviations: FEV1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; Reiff index: bronchiectasis extension score; GGO: Ground Glass Opacities; BE: Bronchiectasis; SD: Standard Deviation; %: percentage.

5.8 DIAGNOSIS OF ASSOCIATED ASTHMA

The collected data were stratified as described in the methods' section. Given the heterogeneity of BE symptoms, we defined the clinical criteria for asthma diagnosis as met only when at least two symptoms were present, with one being either wheezing or chest tightness. Additionally, symptoms had to show variability over time and could not be limited to episodes of acute infections.

Although these criteria are inherently arbitrary, they were designed to minimize the risk of asthma overdiagnosis in cases where symptoms might be solely attributed to BE or transient airway hyperreactivity due to inflammation during exacerbations.

Forty-five subjects (58.4%) presented at least two characteristics symptoms, being one of them wheezing or chest tightness. All these patients described some degree of variability, but 9 (20.0%) were excluded because symptoms only presented during infections.

Therefore, major clinical criteria were fulfilled by 36 patients (46.8%). On the other hand, 46 patients (59.7%) fulfilled minor clinical criteria (family history, aspirin intolerance). Both criteria were met by 18 patients (23.4%).

Regarding functional criteria, it was met only by 4 patients. Six patients (8.0%) had a previous methacholine available, which was negative in all of them.

According to available data, the biological criteria was met by 29 patients. Most patients (24 patients, 82.7%) presented only one of the considered markers, being FeNO >25 ppb in 14 and blood eosinophilia in 10. Only 5 patients (17.3%) showed a combination of both features.

Based on the combination of clinical, functional, and biological characteristics, the cohort was stratified into three groups reflecting the likelihood of asthma comorbidity.

Diagnosis of asthma was confirmed in 3 patients (3.9%); another patient met clinical and functional criteria, but no biological criteria. Anyway, reviewing symptoms, QoL questionnaires and considering the impossibility to perform tests to exclude neutrophilic asthma phenotype (cellular count on sputum), investigators decided to include this patient in the "confirmed asthma group" (total 5.2%).

Twenty patients (26.0%) were allocated in the "suspected asthma" group: all of them fulfilled clinical mayor criteria but had no functional confirmation. Among these, sixteen (80.0%) had family history of asthma, five subjects (25.0%) had atopy confirmed by Phadiatop, while 12 (60.0%) presented elevated eosinophils and/or FeNO.

For the remaining patients, methacholine challenge testing would be required to confirm the diagnosis, particularly in the 12 individuals who exhibited features suggestive of Th2-predominant inflammation.

Finally, in 53 patients (68.8%) asthma was discarded. Indeed, a considerable number of patients exhibited individual features suggestive of asthma, though these were not accompanied by any other supporting criteria (Tab 5.19). In 6 patients, asthma was discarded due to the availability of negative methacholine.

Table 5.19: Asthma features in patients where asthma was excluded.

Criterion	N=53
Clinical mayor	13 (24.5%)
Family history	28 (52.8%)
Allergy	8 (15.1%)
FeNO> 25pbb	10 (18.9%)
Eosinophils ≥ 300	6 (11.3%)
FEV1 variability >20%	13 (24.5%)

Given that only three of the four patients were classified as having "confirmed asthma," the statistical power for analysing this subgroup was very limited. However, their clinical and functional characteristics were comparable to those in the "suspected asthma" category. Therefore, for analytical purposes, we combined the confirmed and suspected cases into a single category of 24 patients and compared this merged group with the "no asthma" group of 53 patients.

Patients with confirmed or suspected asthma had a higher BMI (mean values 26.5 vs 22.6, $p<0.05$). Also, these patients exhibited lower FVC and total lung capacity (TLC) values (Mean postBD FVC 78.6% vs 89.2%, $p<0.05$; mean TLC 84.1% vs 94.6%, $p<0.05$), while the rest of lung function values did not differ between the two groups.

ICS use was significantly higher in the suspected/confirmed asthma group, being reported in 18 out of 24 patients (75%) compared with 23 out of 53 (47.2%) of those in whom asthma had been excluded ($p=0.02$). All 4 patients with confirmed asthma were treated with ICS (100%). No patients in the cohort received OCS or biologic therapies, as ongoing treatment with these agents was an exclusion criterion in our study protocol.

Radiological findings were similar between patients with and without suspected or confirmed asthma. Mild BE (Reiff score) was reported in 55% of patients with suspected/comorbid asthma and in 66% of non-asthmatic patients, although the difference was not statistically significant ($p = 0.56$). No differences were observed on prevalence of emphysema, GGO, BWT, MP and air trapping, though the latter that was more frequently observed in the suspected/confirmed asthma group (83%) than in non-asthmatics (64%)

(p=0.17), On the other hand, they showed no differences in age, BE symptoms, disease severity scores, frequency of exacerbation and prevalence of CBI and *PA* ITab 5.20).

Similarly, QoL questionnaires (including ACT) did not show any significative difference.

Table 5.20: Comparison of results between patients according to asthma diagnosis (confirmed, suspected and excluded

Variable (unit, expression)	Asthma Confirmed n=4	Asthma Suspected n=20	Asthma Excluded n=53	p-value[a]
Age, years, median (IQR)	65.5 (35;79)	65 (47.5; 70)	62 (46; 73)	0.680
Females, n (%)	3 (75.0%)	17 (85.0%)	41 (77.4%)	0.768
BMI kg/m², median (IQR)	26.5 (23.1–28.7)	26.48 (21.44; 30.95)	22.58 (19.9; 25.59)	0.012*
Daily sputum volume ml, median (IQR)	27.5 (4.99–60.0)	10 (4.99; 11.25)	10 (5; 20)	0.357
Sputum colour (Murray score), median (IQR)	2.5 (1–3)	2 (1; 3)	2 (2; 3)	0.835
Total exacerbations n, median (IQR)	1 (0–6)	1 (0; 1.25)	1 (0; 1)	0.446
Mild exacerbations (n), median (IQR)	1 (0–6)	1 (0; 1.25)	1 (0; 1)	0.173
Inhaled corticosteroid	4 (100.0%)	13 (65.0%)	25 (47.2%)	**0.002***
Chronic infection n (%)	3 (75.0%)	8 (42.1%)	22 (42.3%)	0.589
CBI for PA n (%)	3 (75.0%)	8 (47.1%)	20 (39.2%)	0.445
Severity				
FACED Score, median (IQR)	3 (2.2;3.5)	3 (2; 4)	2.5 (2; 4)	0.982
FACED Mild (%, n) **Moderate (%, n)** **Severe (%, n)**	1 (25.0%) 2 (50.0%) 1 (25.0%)	9 (45.0%) 8 (40.0%) 3 (15.0%)	26 (50.0%) 15 (28.9%) 11 (21.1%)	0.541
BSI Score, median (IQR)	7 (4.2;9.2)	5.5 (2; 8)	5 (3; 8)	0.978
BSI Mild (%, n) **Moderate (%, n)** **Severe (%, n)**	1 (25.0%) 1 (25.0%) 2 (50.0%)	9 (45.0%) 7 (35.0%) 4 (20.0%)	20 (38.5%) 23 (44.2%) 9 (17.3%)	0.603
Quality of Life Questionnaire				
LCQ score, median (IQR)	16 (14.5; 18.5)	14 (10; 18)	16 (13.75; 18.5)	0.323
SGRQ score, median (IQR)	40 (41.3; 43.9)	48.2 (32.25; 51.4)	36.26 (25.98; 52.53)	0.624
SGRQ quartile 1st, n (%) **2nd, n (%)** **3rd, n (%)** **4th, n (%)**	0 (0.0%) 3 (100.0%) 0 (0.0%) 0 (0.0%)	4 (22.2%) 7 (38.9%) 6 (33.3%) 1 (5.6%)	8 (17.4%) 24 (52.2%) 12 (26.1%) 2 (4.3%)	0.989
ACT score, median (IQR)	22 (22; 22.5)	22 (19; 24)	22 (19; 25)	0.405
ACT Not controlled n(%) **Poorly controlled n (%)** **Well controlled n (%)**	1 (25.0%) 2 (50.0%) 1 (25.0%)	4 (23.5%) 2 (11.8%) 11 (64.7%)	7 (15.2%) 6 (13.0%) 33 (71.7%)	0.870
CAT score, median (IQR)	19 (19; 19)	19 (14.5; 22)	14 (9; 17)	0.107

CAT Low, n (%) **Medium, n (%)** **High, n (%)** **Very high, n (%)**	0 (0.0%) 1 (100.0%) 0 (0.0%) 0 (0.0%)	2 (13.3%) 7 (46.7%) 5 (33.3%) 1 (6.7%)	12 (33.3%) 18 (50.0%) 5 (13.9%) 1 (2.8%)	0.276
Lung function				
FVC %, mean (± SD)	82.9 (19.8)	77.63 (20.86)	89.19 (19.22)	**0.023***
FEV1 %, median (IQR)	68 (63.8; 84.2)	73.5 (65.45; 86.7)	82.8 (70.6; 97)	0.188
FEV1/FVC %, median (IQR)	70.9 (70.5; 72.2)	75.29 (67.26; 80.3)	75.94 (68.69; 81.96)	0.565
TLC %, median (IQR)	78.6 (71.55; 82)	86.6 (71.95; 96.65)	94.25 (85.12; 102.58)	**0.044***
DLCO/VA %, median (IQR)	92.8 (89.05; 98.55)	109.1 (96.88; 112.37)	97.9 (87.2; 105.2)	0.138
Inflammatory markers				
Eosinophils %, median (IQR)	1.2 (0.85;3.33)	3.5 (1.45; 5.6)	1.5 (0.92; 2.77)	**0.039***
Eosinophils 10^9/L, median (IQR)	0.1 (0.1; 0.22)	0.2 (0.1; 0.4)	0.1 (0.1; 0.2)	**0.012***
FEnO ppb, median (IQR)	34 (30.5; 34.25)	14.5 (10.25; 35.5)	16 (9; 22.25)	0.181
Radiology				
Number of lobes with BE, median (IQR)	5.0 (2–5)	4.5 (2.75; 6)	4 (3; 5)	0.856
Reiff Index, median (IQR)	6.0 (1–8)	6 (2.75; 10.25)	5 (3.75; 8)	0.454
Reiff Mild (1-6) (%, n) **Moderate (7-12) (%, n)** **Severe (13-18) (%, n)**	2 (50.0%) 2 (50.0%) 0 (0.0%)	11 (55.0%) 7 (35.0%) 2 (10.0%)	34 (66.7%) 17 (33.3%) 0 (0.0%)	0.093
Cystic BE, n (%)	1 (25.0%)	1 (5.0%)	8 (15.1%)	0.295
Air trapping, n (%)	2 (66.7%)	18 (94.7%)	34 (87.2%)	0.984
Bronchial thickening, n (%)	3 (75.0%)	18 (90.0%)	44 (86.3%)	0.772
Mucus plugging, n (%)	3 (75.0%)	13 (65.0%)	36 (70.6%)	0.940
GGO, n (%)	4 (100.0%)	9 (45.0%)	23 (44.2%)	1.000
Centrilobular GGO, n (%)	3 (75.0%)	4 (20.0%)	16 (30.2%)	0.564

[a]: p is calculated between asthma confirmed and suspect (n=24) vs excluded (n=53)
*** p < 0.05 considered statistically significant.**
Abbreviations: SD = standard deviation, IQR = interquartile range, BMI = body mass index, FVC = forced vital capacity, FEV1 = forced expiratory volume in 1 second, DLCO = diffusing capacity of the lung for carbon monoxide, VA = alveolar volume, LCQ = Leicester Cough Questionnaire, SGRQ = St. George's Respiratory Questionnaire, ACT = Asthma Control Test, CAT = COPD Assessment Test, BE = bronchiectasis, GGO = ground glass opacity, PA = Pseudomonas aeruginosa, CBI = chronic bacterial infection.

5.9 DIAGNOSIS OF ASSOCIATED COPD

ROSE criteria were met by 7 patients (9.1%). Exposures were confirmed for all of them: 5 were ex-smokers (>10 packs/year), one patient had prolonged exposure to biomasses and one had both smoking history and professional long-term exposure.

Mean FEV1% was 72.2% (SD 19.3; median 67.5%), compared with 81.8% (SD 20.3; median 80.8%) in non-COPD patients, without reaching significance (p=0.28). As expected, considering the diagnostic criteria of the association, FEV1/FVC values were significantly lower in COPD-BE patients (64.5% vs. 75.5%, $p < 0.05$). No other functional differences were observed.

Radiological severity of BE, as measured by Reiff scores, was significantly lower in the COPD-BE group, with 83.3% of patients presenting mild scores compared to 60.9% in the control group ($p < 0.05$). No patient had emphysema on HRCT, while BWT was described in all 7 patients (100%). AT and MP were observed in 6 patients (85.7%), while GGO was present in 3 patients (42.9%). Radiological findings showed increased prevalence of higher Reiff scores in BE-COPD compared with the non-COPD population (Reiff 3rd. However, the small sample size limits the power of the analysis.

Similarly, no significant differences were observed in age, BMI, history or symptoms of BE, BE severity scores (FACED and BSI), inhaled treatments, prevalence of CBI or PA, underlying aetiology, exacerbation rates, QoL, or inflammatory markers (eosinophilia, FeNO, IgE) (Tab 5.21)

Table 5.21: Comparison of results between BE-COPD and non-COPD patients

Variable (unit, expression)	BE-COPD	COPD excluded	p-value
Age at consent, years, median (IQR)	69 (66; 77)	62 (45.25; 70)	0.051
Female, n (%)	5 (71.4%)	56 (80.0%)	0.965
BMI kg/m², median (IQR)	20.83 (20.12; 22.87)	23.7 (20.59; 27.54)	0.253
Daily sputum volume ml, median (IQR)	15 (5; 20)	10 (4.99; 20)	0.802
Sputum colour (Murray score), median (IQR)	2 (1; 2.5)	2 (2; 3)	0.422
Total exacerbations n, median (IQR)	1 (0; 1.5)	1 (0; 1)	0.786
Mild exacerbations n, median (IQR)	1 (0; 1)	1 (0; 1)	0.724
Inhaled corticosteroid, n (%)	5 (71.4%)	37 (52.9%)	0.587
Chronic infection n (%)	4 (57.1%)	37 (54.4%)	**1.000**
CBI for PA n (%)	4 (66.7%)	27 (40.9%)	**0.430**
Severity			
FACED Score, median (IQR)	3 (2; 4)	3 (2; 4)	0.692
FACED Mild (%, n) **Moderate (%, n)** **Severe (%, n)**	3 (42.9%) 2 (28.6%) 2 (28.6%)	33 (47.8%) 23 (33.3%) 13 (18.8%)	0.826
BSI Score, median (IQR)	7 (5; 7.5)	5 (3; 8)	0.33
BSI Mild (%, n) **Moderate (%, n)** **Severe (%, n)**	1 (14.3%) 5 (71.4%) 1 (14.3%)	29 (42.0%) 26 (37.7%) 14 (20.3%)	0.209
Quality of Life Questionnaire			
LCQ score, median (IQR)	19 (16; 19)	15 (12.75; 18)	0.120
SGRQ score, median (IQR)	32.59 (23.81; 40.12)	43.01 (29.88; 51.58)	0.254
SGRQ quartile 1st, n (%) **2nd, n (%)** **3rd, n (%)** **4th, n (%)**	2 (33.3%) 3 (50.0%) 1 (16.7%) 0 (0.0%)	10 (16.4%) 31 (50.8%) 17 (27.9%) 3 (4.9%)	0.699
ACT score, median (IQR)	21.5 (20.25; 23.5)	22 (19; 24)	0.816
ACT Not controlled n(%) **Poorly controlled n (%)** **Well controlled n (%)**	1 (16.7%) 0 (0.0%) 5 (83.3%)	10 (16.4%) 8 (13.1%) 43 (70.5%)	0.634
CAT score, median (IQR)	14.5 (12.75; 16.75)	16 (9.5; 19.5)	0.820
CAT Low, n (%) **Medium, n (%)** **High, n (%)** **Very high, n (%)**	1 (25.0%) 2 (50.0%) 1 (25.0%) 0 (0.0%)	13 (27.1%) 24 (50.0%) 9 (18.8%) 2 (4.2%)	0.970
Lung function			

V1 FVC post %, median (IQR)	82.35 (74.5; 94.62)	89.5 (75; 97.1)	0.838
V1 FEV1 post %, median (IQR)	67.5 (63.52; 84.45)	80.8 (68.5; 96.1)	0.286
V1 FEV1/FVC post %, median (IQR)	67.46 (60.75; 70.36)	77.2 (69.12; 81.9)	0.016
TLC % predicted, median (IQR)	90.4 (71.18; 100.1)	92.4 (81.9; 101)	0.648
DLCO/VA % predicted, median (IQR)	105.7 (87.6; 107.1)	100.1 (87.2; 108)	0.974
Inflammatory markers			
Eosinophils %, median (IQR)	1.6 (1.25; 2.65)	1.8 (0.92; 3.18)	0.970
Eosinophils 10^9/L, median (IQR)	0.1 (0.1; 0.2)	0.1 (0.1; 0.2)	0.763
FEnO ppb, median (IQR)	17 (11; 26)	16 (9.5; 25.5)	0.912
Radiology			
Number of lobes with BE, median (IQR)	4 (2.5; 4.5)	4 (3; 6)	0.628
Reiff Index, median (IQR)	5 (3.5; 5.5)	6 (3; 8)	0.698
Reiff Mild (1-6) (%, n) **Moderate (7-12) (%, n)** **Severe (13-18) (%, n)**	5 (83.3%) 0 (0.0%) 1 (16.7%)	42 (60.9%) 26 (37.7%) 1 (1.4%)	**0.024***
Cystic BE, n (%)	1 (14.3%)	14 (20.0%)	0.884
Air trapping, n (%)	6 (100.0%)	48 (87.3%)	0.799
Bronchial thickening, n (%)	7 (100.0%)	59 (86.8%)	0.678
Mucus plugging, n (%)	6 (85.7%)	46 (67.7%)	0.578
GGO, n (%)	3 (42.9%)	31 (44.9%)	1.000
Centrilobular GGO, n (%)	1 (14.3%)	20 (28.6%)	0.716

*** p < 0.05 considered statistically significant.**
Abbreviations: SD = standard deviation, IQR = interquartile range, BMI = body mass index, FVC = forced vital capacity, FEV1 = forced expiratory volume in 1 second, DLCO = diffusing capacity of the lung for carbon monoxide, VA = alveolar volume, LCQ = Leicester Cough Questionnaire, SGRQ = St. George's Respiratory Questionnaire, ACT = Asthma Control Test, CAT = COPD Assessment Test, BE = bronchiectasis, GGO = ground glass opacity, PA = Pseudomonas aeruginosa, CBI = chronic bacterial infection.

5.10 DIAGNOSIS OF ASSOCIATED CRS

Diagnosis of associated CRS was primarily based on clinical characteristics, with imaging or endoscopic confirmation when available. Complete data were available for 73 patients.

Among them, 20 patients (27.4%) reported the presence of at least two symptoms compatible with CRS for more than 12 weeks.

Among patients with no UAS, 41 individuals (54.7%) were classified as negative for CRS (Group F). An additional 3 patients, previously treated endoscopically for CRS, had remained symptom-free since surgery and were categorized as Group E.

In 9 patients (12.0%), UAS were present; however, the duration, location, or combination of symptoms did not fulfil the diagnostic criteria for CRS (Group D).

Associated CRS was ultimately diagnosed in 23 patients (31.5%), including the 3 patients previously classified in Group E. Among those with CRS, 11 patients (34.4%) received a clinical diagnosis without confirmation by CT or endoscopy, while 5 patients (15.6%) had instrumentally confirmed CRS. Additionally, 4 patients (12.5%) were identified as having CRS with nasal polyps (CRSwNP).

Table 5.22: Descriptive comparison of results between CRS subgroups

Variable (unit, expression)	Clinical CRS n=11	Confirmed CRS n=5	CRSwNP n=4	Past CRS n=3
Age, years, mean (± SD)	53.18 (20.5)	70.6 (9.07)	52.25 (18.39)	48.67 (7.51)
Females, n (%)	8 (72.73%)	4 (80%)	3 (75%)	2 (66.67%)
BMI kg/m², mean (± SD)	22.57 (4.56)	22.48 (1.56)	25.72 (1.43)	23.29 (3.14)
Daily sputum volume ml, mean (± SD)	25.45 (18.64)	17 (7.59)	30 (18.26)	6.66 (2.89)
Sputum colour (Murray score), mean (± SD)	2 (2; 2.75)	2 (1; 2)	2.5 (2; 3)	2 (1.5; 3)
Total exacerbations n, mean (± SD)	1.18 (1.4)	1 (1.22)	1 (0)	4 (5.2)
Mild exacerbations n, mean (± SD)	7 (63.64%)	4 (80%)	3 (75%)	1 (33.33%)
Inhaled corticosteroid	6 (54.55%)	3 (60%)	3 (75%)	**1 (50%)**
Chronic infection n (%)	4 (36.36%)	3 (60%)	2 (50%)	**1 (50%)**
CBI for PA n (%)				
FACED Score, mean (± SD)	2.73 (1.95)	2.6 (2.7)	2.5 (0.58)	2.33 (0.58)
FACED Mild (%, n)	5 (45.45%)	3 (60%)	2 (50%)	2 (66.67%)
Moderate (%, n)	5 (45.45%)	1 (20%)	2 (50%)	1 (33.33%)
Severe (%, n)	1 (9.09%)	1 (20%)	0 (0%)	0 (0%)

BSI Score, mean (± SD)	5.09 (3.59)	5.8 (3.7)	5.25 (2.5)	3.67 (2.52)
BSI Mild (%, n) **Moderate (%, n)** **Severe (%, n)**	5 (45.45%) 4 (36.36%) 2 (18.18%)	2 (40%) 2 (40%) 1 (20%)	1 (25%) 3 (75%) 0 (0%)	2 (66.67%) 1 (33.33%) 0 (0%)
Quality of Life Questionnaire				
LCQ score, mean (± SD)	14.66 (3.53)	16.05 (2.76)	16 (2.83)	16 (2.83)
SGRQ score, mean (± SD)	42.73 (17.83)	38 (15.22)	45.14 (7.19)	45.14 (7.19)
SGRQ quartile 1st, n (%) **2nd, n (%)** **3rd, n (%)** **4th, n (%)**	1 (9.09%) 6 (54.55%) 3 (27.27%) 1 (9.09%)	1 (25%) 2 (50%) 1 (25%) 0 (0%)	0 (0%) 3 (75%) 1 (25%) 0 (0%)	0 (0%) 1 (50%) 0 (0%) 1 (50%)
ACT score, mean (± SD)	20.55 (4.59)	21.4 (3.58)	22 (1.41)	22 (1.41)
ACT Not controlled n(%) **Poorly controlled n (%)** **Well controlled n (%)**	0 (0%) 3 (27.27%) 8 (72.73%)	0 (0%) 1 (20%) 4 (80%)	0 (0%) 0 (0%) 4 (100%)	2 (22.22%) 0 (0%) 7 (77.78%)
CAT score, mean (± SD)	15.14 (6.2)	21.67 (7.09)	17.33 (4.51)	16.88 (10.44)
CAT Low, n (%) **Medium, n (%)** **High, n (%)** **Very high, n (%)**	1 (14.29%) 5 (71.43%) 1 (14.29%)	0 (0%) 1 (33.33%) 2 (66.67%)	0 (0%) 2 (66.67%) 1 (33.33%)	2 (25%) 4 (50%) 1 (12.5%)
Lung function				
FVC %, mean (± SD)	80.73 (31.27)	102.7 (9.1)	77.95 (11.37)	85.42 (12.01)
FEV1 %, mean (± SD)	84.56 (27.46)	97.72 (11.67)	68.38 (8.45)	92.7 (4.2)
FEV1/FVC %, mean (± SD)	73.87 (11.17)	79.06 (7.77)	70.21 (5.95)	77.99 (6.24)
TLC %, mean (± SD)	94.59 (6.39)	88.6 (11.86)	94.78 (22.78)	94.78 (22.78
DLCO/VA %, mean (± SD)	96.36 (14.32)	102 (8.02)	90.38 (8.4)	90.38 (8.4)
Inflammatory markers				
Eosinophils %, mean (± SD)	3.17 (3.25)	4.18 (3.16)	2.45 (3.06)	3.33 (3.82)
Eosinophils 10^9/L, mean (± SD)	0.19 (0.18)	0.26 (0.22)	0.15 (0.17)	0.2 (0.26)
FEnO ppb, mean (± SD)	20.45 (20.69)	33.75 (13.1)	27 (13.04)	17 (11.27)
Radiology				
Number of lobes with BE, mean (± SD)	3.27 (1.85)	3.4 (1.95)	3.5 (1.91)	4.33 (1.53)
Reiff Index, mean (± SD)	4.64 (3.14)	3.2 (2.17)	6 (4.55)	6.33 (4.93)
Reiff Mild (1-6) (%, n) **Moderate (7-12) (%, n)** **Severe (13-18) (%, n)**	7 (63.64%) 4 (36.36%) 0 (0.00%)	5 (100%) 0 (0.00%) 0 (0.00%)	3 (75%) 1 (25%) 0 (0.00%)	2 (66.67%) 1 (33.33%) 0 (0%)
Cystic BE, n (%)	2 (18.18%)	0 (0%)	1 (25%)	0 (0%)
Air trapping, n (%)	6 (75%)	3 (75%)	3 (100%)	2 (66.67%)

Bronchial thickening, n (%)	8 (80%)	5 (100%)	4 (100%)	2 (66.67%)
Mucus plugging, n (%)	6 (60%)	3 (60%)	3 (75%)	1 (33.33%)
GGO, n (%)	3 (27.27%)	0 (0%)	1 (25%)	2 (66.67%)
Centrilobular GGO, n (%)	1 (9.09%)	0 (0%)	1 (25%)	2 (66.67%)

*** p < 0.05 considered statistically significant.**
Abbreviations: CRS: chronic rhinosinusitis, CRSwNP: chronic rhinosinusitis with nasal polyps, SD = standard deviation, IQR = interquartile range, BMI = body mass index, FVC = forced vital capacity, FEV1 = forced expiratory volume in 1 second, DLCO = diffusing capacity of the lung for carbon monoxide, VA = alveolar volume, LCQ = Leicester Cough Questionnaire, SGRQ = St. George's Respiratory Questionnaire, ACT = Asthma Control Test, CAT = COPD Assessment Test, BE = bronchiectasis, GGO = ground glass opacity, PA = Pseudomonas aeruginosa, CBI = chronic bacterial infection.

Patients with CRS showed significantly higher sputum volume compared to those without this comorbidity (p = 0.024). They also exhibited slightly lower radiological extension, with a lower average number of lobes affected by bronchiectasis (3.4, SD 1.76 vs. 4.22, SD 1.69; p = 0.050) and lower Reiff scores (4.64, SD 3.34 vs. 6.29, SD 3.34; p = 0.044). On the other hand, no significant differences were found between patients with and without CRS regarding age, bronchiectasis severity, exacerbation rate, FeNO levels, asthma diagnosis or suspicion, and lung function (Tab 5.23)

Tab 5.23: comparison of results between patients with and without CRS diagnosis

Variable (unit, expression)	CRS-BE n=23	CRS excluded n=54	p value
Age, years, median (IQR)	55.72 (17.89)	58.66 (16.19)	0.511
Females, n (%)	19 (76.0%)	40 (80.0%)	0.921
BMI kg/m², median (IQR)	22.91 (3.53)	24.83 (6.06)	0.331
Daily sputum volume ml, median (IQR)	22.2 (16.34)	16.08 (19.44)	**0.024***
Sputum colour (Murray score), mean (± SD)	2 (2; 3)	2 (1.25; 3)	0.800
Total exacerbations n, median (IQR)	1.48 (2.24)	1.16 (1.6)	0.311
Mild exacerbations n, median (IQR)	16 (64.0%)	24 (48.0%)	0.287
Inhaled corticosteroid	14 (58.3%)	27 (55.1%)	0.992
Chronic infection n (%)	11 (45.8%)	20 (43.5%)	1.000
CBI for PA n (%)			
FACED Score, median (IQR)	2.6 (1.85)	2.86 (1.71)	0.445

FACED Mild (%, n) **Moderate (%, n)** **Severe (%, n)**	13 (52.0%) 9 (36.0%) 3 (12.0%)	23 (46.9%) 14 (28.6%) 12 (24.5%)	0.437
BSI Score, median (IQR)	5 (3.12)	5.84 (3.51)	0.301
BSI Mild (%, n) **Moderate (%, n)** **Severe (%, n)**	11 (44.0%) 11 (44.0%) 3 (12.0%)	19 (38.8%) 19 (38.8%) 11 (22.4%)	0.555
Quality of Life Questionnaire			
LCQ score, median (IQR)	15.18 (3.16)	15.23 (4.1)	0.648
SGRQ score, median (IQR)	43.94 (16.58)	40.09 (16.34)	0.383
SGRQ quartile 1st, n (%) **2nd, n (%)** **3rd, n (%)** **4th, n (%)**	2 (9.5%) 12 (57.1%) 5 (23.8%) 2 (9.5%)	9 (20.0%) 22 (48.9%) 13 (28.9%) 1 (2.2%)	0.400
ACT score, median (IQR)	21 (3.78)	21.14 (3.97)	0.680
ACT Not controlled n(%) **Poorly controlled n (%)** **Well controlled n (%)**	1 (4.5%) 4 (18.2%) 17 (77.3%)	10 (22.7%) 4 (9.1%) 30 (68.2%)	0.130
CAT score, median (IQR)	16.93 (6.02)	15.16 (7.95)	0.401
CAT Low, n (%) **Medium, n (%)** **High, n (%)** **Very high, n (%)**	1 (7.1%) 9 (64.3%) 4 (28.6%) 0 (0.0%)	13 (34.2%) 17 (44.7%) 6 (15.8%) 2 (5.3%)	0.160
Lung function			
FVC %, mean (± SD)	84.54 (24.8)	86.37 (17.42)	0.436
FEV1 %, median (IQR)	84.02 (23.16)	79.49 (19.05)	0.411
FEV1/FVC %, median (IQR)	75.51 (9.42)	74.19 (10.18)	0.587
TLC %, median (IQR)	92.76 (12.85)	91.33 (20.47)	0.567
DLCO/VA %, median (IQR)	94.59 (12.26)	99.57 (14.64)	0.183
Inflammatory markers			
Eosinophils %, median (IQR)	3.08 (3.04)	2.17 (1.52)	0.824
Eosinophils 10^9/L, median (IQR)	0.19 (0.18)	0.17 (0.18)	0.920
FEnO ppb, median (IQR)	22.29 (17.11)	20.18 (15.1)	0.814
Radiology			
Number of lobes with BE, median (IQR)	3.4 (1.76)	4.22 (1.69)	0.050

Reiff Index, median (IQR)	4.64 (3.34)	6.29 (3.34)	**0.044***
Reiff Mild (1-6) (%, n) **Moderate (7-12) (%, n)** **Severe (13-18) (%, n)**	19 (76.0%) 6 (24.0%) 0 (0.0%)	27 (56.2%) 19 (39.6%) 2 (4.2%)	0.199
Cystic BE, n (%)	3 (12.0%)	12 (24.0%)	0.347
Air trapping, n (%)	16 (80.0%)	36 (92.3%)	0.338
Bronchial thickening, n (%)	20 (83.3%)	44 (89.8%)	0.682
Mucus plugging, n (%)	14 (58.3%)	37 (75.5%)	0.218
GGO, n (%)	8 (32.0%)	25 (51.0%)	0.190
Centrilobular GGO, n (%)	4 (16.0%)	16 (32.0%)	0.230

*** p < 0.05 considered statistically significant.**
Abbreviations: CRS: chronic rhinosinusitis, SD = standard deviation, IQR = interquartile range, BMI = body mass index, FVC = forced vital capacity, FEV1 = forced expiratory volume in 1 second, DLCO = diffusing capacity of the lung for carbon monoxide, VA = alveolar volume, LCQ = Leicester Cough Questionnaire, SGRQ = St. George's Respiratory Questionnaire, ACT = Asthma Control Test, CAT = COPD Assessment Test, BE = bronchiectasis, GGO = ground glass opacity, PA = Pseudomonas aeruginosa, CBI = chronic bacterial infection.

5.11 PATIENTS WITH PURE BE VS BE WITH COMORBIDITIES

Overall, patients with pure bronchiectasis, meaning with no comorbidity confirmed or highly suspected, were 33 (42.9%).

Among those with comorbidities, 34 (77.3% of the subgroup, 44.1% of the cohort) had only one AWD apart from BE, while 10 (22.7%; 12.8% of the entire study population) had two confirmed or suspected comorbidities (Fig 5.5).

No differences were observed between pure patients and those with at least one concomitant AWD in terms of clinical presentation, microbiology, lung function, severity, exacerbations or QoL. Results of the comparison are reported in Tab 5.24.

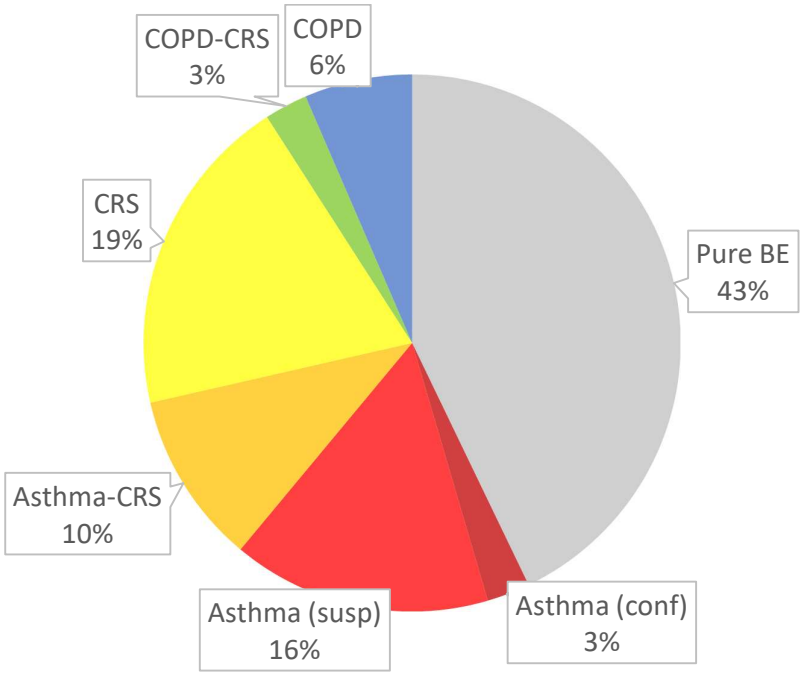


Figure 5. 5 Distribution of comorbidities in our BE cohort.

Abbreviations: CRS: Chronic Rhinosinusitis, CODP: Chronic obstructive pulmonary disease, Susp: suspected, Conf: confirmed. *Note: Asthma-CRS includes both suspected and confirmed asthma patients.*

Table 5.24: Comparison of results between patients with any BE comorbidity (asthma, COPD, CRS) and pure BE

Variable (unit, expression)	BE with COMORBIDITIES	Pure BE	p-value
Age at consent, years, median (IQR)	63 (46; 71)	63 (47; 70)	0.877
Female, n (%)	75.0% (33/44)	75.0% (25/33)	0.441
BMI, median (IQR)	24.51 (20.88; 27.72)	22.66 (19.9; 25.95)	0.157
Daily sputum volume, mL, median (IQR)	10 (5; 21.25)	10 (4.99; 20)	0.400
Sputum colour (Murray score), median (IQR)	2 (1.5; 3)	2 (2; 3)	0.885
Total exacerbations n, median (IQR)	1 (0; 1)	1 (0; 2)	0.671
Mild exacerbations n, median (IQR)	1 (0; 1)	1 (0; 1)	0.375
Inhaled corticosteroid n, (%)	63.64%	42.42%	0.106
Chronic infection n (%)	21 (48.84%)	16 (62.5%)	0.347
CBI for PA n (%)	20 (45%)	40.62%	0.894
Severity			
FACED Score, median (IQR)	3 (2; 4)	3 (2; 4.25)	0.767
FACED Mild (%, n) Moderate (%, n) Severe (%, n)	3 (42.86%) 2 (28.57%) 2 (28.57%)	33 (47.83%) 23 (33.33%) 13 (18.84%)	0.826
BSI Score, mean (± SD)	5.34 (3.16)	5.94 (3.65)	0.460
BSI Mild (%, n) Moderate (%, n) Severe (%, n)	1 (14.29%) 5 (71.43%) 1 (14.29%)	29 (42.03%) 26 (37.68%) 14 (20.29%)	0.209
Quality of Life Questionnaire			
LCQ score, mean (± SD)	17.42 (2.97)	15.09 (3.88)	0.120
SGRQ score, mean (± SD)	34.17 (13.67)	41.64 (16.7)	0.254
SGRQ quartile 1st, n (%) 2nd, n (%) 3rd, n (%) 4th, n (%)	2 (33.33%) 3 (50%) 1 (16.67%) 0 (0%)	10 (16.39%) 31 (50.82%) 17 (27.87%) 3 (4.92%)	0.699
ACT score, mean (± SD)	21.5 (2.35)	21.08 (3.98)	0.816
ACT Not controlled n(%) Poorly controlled n (%) Well controlled n (%)	1 (16.67%) 0 (0%) 5 (83.33%)	10 (16.39%) 8 (13.11%) 43 (70.49%)	0.634
CAT score, mean (± SD)	16.62 (7.48)	16.62 (7.48)	0.288
CAT Low, n (%) Medium, n (%) High, n (%) Very high, n (%)	1 (25%) 2 (50%) 1 (25%) 0 (0%)	13 (27.08%) 24 (50%) 9 (18.75%) 2 (4.17%)	0.970
Lung function			
V1 FVC post %, mean (± SD)	86.2 (16.23)	85.9 (20.25)	0.838
V1 FEV1 post %, mean (± SD)	72.17 (19.28)	81.83 (20.33)	0.286

V1 FEV1/FVC post %, mean (± SD)	64.47 (7.77)	75.45 (9.54)	0.016
TLC % predicted, mean (± SD)	86.45 (17.66)	91.95 (18.58)	0.648
DLCO/VA % predicted, mean (± SD)	97.98 (12.21)	98.18 (14.25)	0.974
Inflammatory markers			
Eosinophils %, mean (± SD)	2.23 (1.76)	2.6 (2.39)	0.970
Eosinophils 10^9/L, mean (± SD)	0.13 (0.08)	0.19 (0.19)	0.763
FEnO ppb, mean (± SD)	26.71 (29.4)	20.16 (13.67)	0.912
Radiology			
Number of lobes, median (IQR)	4 (2; 5)	4.5 (3; 6)	0.187
Reiff index, median (IQR)	5 (2; 7.25)	6 (4; 8)	0.249
Reiff Mild (1-6) (%, n) Moderate (7-12) (%, n) Severe (13-18) (%, n)	5 (83.33%) 0 (0%) 1 (16.67%)	42 (60.87%) 26 (37.68%) 1 (1.45%)	0.024*
Cystic BE, n (%)	20.4% (9/44)	20.4% (7/32)	0.500
Air trapping, n (%)	6 (100%)	48 (87.27%)	0.799
Bronchial thickening, n (%)	7 (100%)	59 (86.76%)	0.678
Mucus plugging, n (%)	6 (85.71%)	46 (67.65%)	0.578
GGO, n (%)	3 (42.86%)	31 (44.93%)	1.000
Centrilobular GGO, n (%)	1 (14.29%)	20 (28.57%)	0.716

*** p < 0.05 considered statistically significant.**
Abbreviations: COPD: chronic obstructive pulmonary disease, CRS: chronic rhinosinusitis, SD = standard deviation, IQR = interquartile range, BMI = body mass index, FVC = forced vital capacity, FEV1 = forced expiratory volume in 1 second, DLCO = diffusing capacity of the lung for carbon monoxide, VA = alveolar volume, LCQ = Leicester Cough Questionnaire, SGRQ = St. George's Respiratory Questionnaire, ACT = Asthma Control Test, CAT = COPD Assessment Test, BE = bronchiectasis, GGO = ground glass opacity, PA = Pseudomonas aeruginosa, CBI = chronic bacterial infection.

6. DISCUSSION

6.1 THE DEFINITION ISSUE

"*The limits of my language means the limits of my world.*"(Ludwig Wittgenstein)(240).

Philosophers from all eras have been debating about the power of words, not only as an instrument to describe reality, but also to influence and manipulate it.

In science and medicine, precision in the use of terms is not merely an academic concern but a fundamental requirement for accurate clinical practice. Misclassifying patients' signs, symptoms, or diseases can lead to significant consequences in their clinical management. However, medical definitions are not written in stone; they are often revised and debated as new research and clinical experiences yield fresh insights. While some debates may seem less critical than others, they are essential to maintaining the rigor that evidence-based medicine demands.

This is the case of the term "overlap". Since the first appearance of the definition "asthma and COPD overlap (ACO) syndrome", the respiratory science community has debated the necessity and appropriateness of creating a new pathological entity to describe the overlapping features of these two well-known conditions. ACO supporters highlight how this term identifies a distinct group of patients with unique characteristics, symptoms, genetics and indication of treatment (241). Conversely, critics contend that the term oversimplifies the complex relationship between asthma and COPD, grouping together patients with diverse presentations and needs, thereby neglecting the specificities of each underlying condition(242). Today the definition is rarely used as definitions of asthma and COPD have also been changing.

In the case of BE and associated respiratory conditions, things are yet more complicated by the lack of reliable evidence. In fact, as reported in the "Introduction" chapter, available data about the association of BE and other AWD is limited and primarily derived from registries and retrospective studies, not enough to support the identification of a distinct clinical entity that shares features of both diseases. Therefore, in this thesis, the candidate has chosen not to use the term "overlap." Instead, the terms "comorbidities" and "coexistence" have been used.

6.2 DEMOGRAPHIC DESCRIPTION AND BE CHARACTERIZATION

Our study enrolled 77 patients with bronchiectasis, with clear predominance of women, most of them with mild and moderate disease. Chronic cough was the most common of chronic symptoms, severely affecting at least a quarter of patients and significantly

impacting social life, even among those with a milder symptom burden. Two thirds of participants referred daily expectoration, mostly mucopurulent or purulent. Dyspnoea, on the other hand, was less common and mild when reported. Most patients reported at least one exacerbation during the previous year, even though only few of them had needed secondary care or hospitalization.

Most of the cohort had chronic respiratory treatment. Inhaled treatments were the most common, especially ICS/LABA, that was used by approximately half of the patients. Antibiotic burden was also important: 20% of patients received chronic inhaled antibiotic treatment, while oral azithromycin was chronically prescribed with immunomodulatory purpose to 40% of them. On the other hand, physiotherapy, one of the cornerstones of BE treatment, was performed regularly by approximately 40% of subjects, but almost half of the entire study population had never been referred to respiratory rehabilitation.

The composition of our study population is heterogeneous and reflects the fact we deliberately adopted broad inclusion criteria and restricted exclusion criteria only to those conditions that could clearly bias the results. This approach allowed us to evaluate airway involvement and comorbidities in a real-life context, rather than within an artificially homogeneous and selectively ideal population.

We acknowledge that this heterogeneity may reduce the statistical power and internal consistency of our findings. However, we believe this limitation is counterbalanced by the consistency of our results with available literature. Moreover, the applicability of our findings to day-by-day clinical practice strengthens the study's value as a tool for understanding the implications and diagnostic challenges of airway comorbidities.

In particular, the composition of our sample reflects the characteristics of the entire population accessing our outpatient clinic. Although there is a common predominance of females in BE international cohorts (32,42,227), it could be that the excessive rate of women in our population reflects their greater willingness to participate in research studies.

This aligns with previous findings suggesting that women are more likely to respond to surveys and studies(243–245).

Notably, the prevalence of rare aetiologies in our cohort, such as primary immunodeficiencies and PCD was relatively high compared with those reported in literature(32,147,187,227). This likely reflects the fact that our Clinic serves as reference centre for most rare diseases, leading to a higher proportion of patients with these conditions in follow-up compared to the prevalence typically reported.

On the other hand, participants in our study exhibited milder disease compared to what is reported in the literature, as reflected in clinical scores, frequency of exacerbations, and hospitalization rates. Despite broad inclusion criteria, the mandatory 4-week stability period prior to inclusion may have been more challenging for patients with severe disease. Additionally, more severe patients in our clinic tend to be older, have greater mobility limitations, are more dependent on caregivers, face difficulties performing lung function tests, or are already enrolled in clinical trials offering potential treatment benefits.

It is also important to highlight that exacerbation data in our study were not investigator-confirmed. They referred to the year preceding enrolment and were based on patient self-report and/or verification of antibiotic prescriptions in electronic pharmacy records when available. This represents a potential source of bias, as patients and primary care physicians may have used criteria different from those defined by our protocol, possibly leading to under- or overestimation of exacerbation frequency. To account for this limitation, we decided to use both the BSI and FACED scores to stratify disease severity, given that only the BSI incorporates exacerbation frequency. The good correlation observed between the two scoring systems suggests that any inaccuracies in exacerbation reporting did not significantly compromise the robustness of the severity assessment.

Levels of dyspnoea and percentage of patients with minimal or absent expectoration were consistent with previously reported data, while our sample showed higher degrees of purulence according to the Murray Sputum Scale, as well as greater daily sputum volumes in a larger proportion of patients. Data from the EMBARC registry indicate that approximately 30% of nearly 14,000 patients reported minimal expectoration. Among these, sputum was mucoid in 28.2% (average daily production of 10 ml), mucopurulent in 27.8% (average 15 ml/day), purulent in 12.9% (average 20 ml/day), and severely purulent in less than 1% (producing >30 ml/day)(246). This difference could be attributed to the higher proportion, in our study, of patients with aetiologies traditionally associated with greater sputum production, such as PCD. Also, this apparent contradiction, a less severe population with a higher burden of sputum production, may be related to follow-up duration. Most of our patients have been under follow-up for over 5 years, during which time treatment may have been optimized, and they could have developed better self-management skills, leading to fewer exacerbations despite a significant symptomatic burden. This is supported by evidence from several chronic conditions, which has shown that optimal self-management, greater disease awareness, and patient empowerment can lead to improved clinical outcomes (247,248). Apart from sputum production, cough is another key symptom in BE patients, both for its clinical relevance and its potential impact on quality of life. The LCQ is

a valuable tool for the multidimensional assessment of cough, validated across various respiratory conditions, including BE(249). In our cohort, both the overall LCQ score and the scores of individual domains were consistent with those reported in previously published BE studies(249,250). Notably, our findings closely align with those of the Spanish BE cohort used to validate the Spanish version of the LCQ. This similarity is particularly relevant, as quality of life questionnaires may be influenced by geographic, cultural, and social factors(251).

Although these studies have reported a correlation between disease severity and LCQ scores, we observed correlation only with BSI categories, not with FACED in our cohort (respectively p=0.031; p=0.182). This partial correlation might be attributed, at least in part, to the relatively small sample size and the limited number of patients with severe disease.

Despite being a valuable tool for cough assessment, particularly in clinical research, the LCQ is often impractical and very rarely performed in routine clinical visits. Its administration requires a time investment that is rarely feasible within the limited duration of a standard outpatient visit (typically 10–15 minutes), during which multiple signs and symptoms must be assessed simultaneously. Moreover, patients are not always willing to complete the questionnaire repeatedly, especially when multiple instruments are administered during the same visit, as these are time consuming.

To identify a more pragmatic alternative for clinical purposes, we explored the use of a single-question item with three response options to assess cough frequency. This simplified approach showed good correlation with the LCQ score ($p<0.001$). Although highly subjective and lacking in detailed information regarding symptom characteristics and impact, it is quick and easy to administer, can be routinely integrated into standard clinical interviews, and may support the identification of symptom changes over time.

We aimed to evaluate whether the frequency and distribution of symptoms in our population may have influenced the widespread use of inhaled therapies in the majority of the cohort. In fact, according to European guidelines, the indication for BD use in BE is limited to the presence of breathlessness, to improve tolerance to physiotherapy and inhaled ATBs, or in case of known respiratory comorbidities such as asthma or COPD(43). In our cohort, the reasons guiding the prescription and selection of respiratory treatments prior to enrolment could not be retrieved and can only be retrospectively speculated. While all 56 patients had at least one indication for BD treatment, the choice of ICS/LABA in most of them remains unclear. In fact, current guidelines do not recommend ICS/LABA in BE patients without asthma, although recent evidence suggests potential benefit in patients with peripheral

eosinophilia (43,122,252). However, it is unlikely that such evidence influenced treatment decisions, as it was published after patient enrolment.

Moreover, ICS overuse despite the absence of clear indications is already a recognised issue: in the EMBARC database, 32.7% of patients without other airway comorbidities had been prescribed ICS, as well as the 39% of the patients included in the USA registry and the 66% of Spanish patients included in the Spanish registry RIBRON(32,144,227). These patients were generally more severe, with worse lung function and higher BSI scores(227). Similarly, in our cohort, patients receiving ICS showed higher FACED scores ($p=0.006$), greater sputum volume ($p=0.022$), and a higher prevalence of chronic infection ($p<0.001$), although no differences were observed for BSI scores, cough, dyspnoea, lung function or CBI for PA.

It is possible that increased disease severity, in the absence of treatments capable of halting disease progression, led clinicians to escalate inhaled therapy, even if the choice of ICS specifically is still not supported by scientific evidence so far in BE. Additionally, at the time of data collection the reason for starting ICS in the previous years had not been reported and their potential effect on long-term symptoms could not be assessed.

On the other hand, the use of inhaled ATB in our cohort was significantly more frequent than reported in other series, such as EMBARC (7.7%) and an Indian cohort (4%), but aligned with the rate observed in the Spanish registry (19.5%). Despite the absence of a formal indication, in Spain the prescription and reimbursement of inhaled antibiotics in BE is subject to fewer restrictions, particularly in reference centres where their use is traditional since a couple of decades. Conversely, in many other European and non-European countries, inhaled antibiotics remain either unavailable, prohibitively expensive, or limited to CF patients, which likely contributes to their lower prescription rates.

Surprisingly, the use of azithromycin in our cohort was almost twice as high as that reported in the literature(32,147,187,227). Our Centre has a long-standing experience with chronic macrolide therapy in BE and Cystic Fibrosis patients, which may have contributed to its more frequent use. According to current guidelines, azithromycin is recommended in patients experiencing at least two (Spanish guidelines) or three (European guidelines) exacerbations per year, as it has been shown to reduce exacerbation frequency in BE(43,253,254).

As for other treatments, we were unable to assess the appropriateness of the initial azithromycin prescriptions in our cohort. However, it is possible that its use contributed to

better disease control, potentially reducing the number of annual exacerbations and influencing the overall severity profile of the population.

Physiotherapy was reported in a lower proportion of patients than observed in other series, despite the rate of patients that had been referred to respiratory rehabilitation was similar (32,227). It is important to notice that access to physiotherapy in our centre is not direct. In fact, our hospital does not have a dedicated physiotherapist working in the BE clinic as in other countries, but a patient referral to the Rehab Department is required(255).

The lower prevalence of patients actively performing airway clearance techniques, despite having received appropriate instruction, is likely due to poor adherence.

Physiotherapy interventions can be time-consuming, physically demanding, and disruptive to daily routines, all of which can significantly affect a patient's willingness and ability to comply. Additionally, the relatively stable condition and lower severity of our patient cohort, compared to those in other published studies, may account for the reduced need for airway clearance techniques in this population.

Finally, the use of hypertonic saline in our cohort was comparable to that reported in the EMBARC registry (8%), but significantly higher than in the Spanish registry (2.5%). Once again, familiarity with this treatment and the ease of prescription within our hospital setting may have contributed to its increased use.

6.3 ASTHMA, COPD AND CRS: CLINICAL EVALUATION

6.3.1 ASTHMA SYMPTOMS

Almost all patients reported having experienced at least one symptom typically associated with asthma throughout their life. Between *asthma-like symptoms*, cough was the most frequently reported symptom (80% of patients), followed by wheezing, which was observed in more than 60% of the cohort and was present in 50% of those cases during the month preceding study enrolment. Sudden onset of dyspnoea and chest tightness were reported by approximately one third of the cohort.

Although these symptoms were commonly triggered by respiratory infections, a substantial proportion of patients (n:37, 48%) also experienced them in stable conditions. In a considerable number of cases (45%), symptoms occurred only upon awakening, at night, or in response to various environmental triggers.

Current exposure to inhalants potentially capable of inducing airway hyperreactivity was reported by half of the patients, although no clear association with symptom presence was identified. This suggests that symptoms in our patients are not secondary to external causes, but due to other factors correlated with the primary disease.

The high prevalence of *wheezing* in our cohort is surprising. While wheezing is frequently listed among the common symptoms of BE, it is rarely highlighted in studies on BE patients, nor it is consistently investigated in registries or databases, including those from Europe and Spain. In a 2024 systematic review on the clinical and socio-economic burden of BE, wheezing was mentioned in only 15 out of 338 studies analysed, with prevalence varying widely from 15% to 65% (256). Eden and colleagues found significant variation in wheezing prevalence across different aetiologies: it was reported in 70% of PCD patients, but in less than a third of those with BE secondary to AATD (26%), idiopathic BE (29%), or BE due to CVID (33%) (257).

Similarly, *chest tightness* is a symptom that is difficult to define objectively and can be influenced by extra-respiratory factors such as cardiac conditions, anxiety, or pneumothorax. Additionally, the way chest symptoms are described in questionnaires, using terms such as 'tightness,' 'pain,' or 'oppression', may lead to confusion and inconsistent reporting by patients. Even in asthma, this symptom remains underexplored. A 'Chest Tightness Variant' (CTV) of asthma has been proposed, characterized by chest tightness in the absence of other classic asthma symptoms(258). However, there is limited evidence supporting the validity of this phenotype, and the prevalence of chest tightness is infrequently reported in clinical studies(259). To our knowledge, no previous studies have specifically assessed the presence and significance of chest tightness or sudden dyspnoea in patients with BE.

Although these symptoms are typically associated with asthma and bronchospasm, we excluded patients with a previously known co-diagnosis of asthma from our study. Furthermore, even accounting for the potential underdiagnosis of asthma, the prevalence of these symptoms in our BE cohort is substantially higher than the reported prevalence of asthma in the European BE registry(122). This suggests that such symptoms may be driven by pathophysiological mechanisms distinct from the classic bronchial smooth muscle constriction seen in asthma. For example, they may be related to BE-specific factors such as reduced bronchial diameter due to mucus plugging or transient bronchial wall thickening during exacerbations. This hypothesis could also explain the considerable variability in the recurrence of these symptoms within the same patient over time.

Nevertheless, data on this phenomenon in BE are currently insufficient. We cannot rule out a more frequent involvement of bronchial smooth muscle in some BE patients, or the possibility of underdiagnosed comorbid asthma. In fact, the lack of a standardized definition of asthma within the context of BE complicates the ability to draw definitive conclusions. More consensus and targeted research are clearly needed to improve the understanding and management of BE patients presenting with these overlapping clinical features.

6.3.2 COPD: SMOKING AND OTHER EXPOSURES

While asthma clinical evaluation in our study was mainly directed at symptoms description, the assessment of COPD was centred around identifying exposures that may contribute to the development of chronic bronchial obstruction, as typical COPD chronic symptoms are not distinguishable from BE presentation (dyspnoea, cough, etc). In addition, previous or current smoking was reported only in one fifth of the cohort; however, only cumulative exposure was equal or superior to 10 pack-years only in half of them, representing approximately 10% of the total sample. An even smaller proportion of patients (less than 8%) reported occupational exposure to noxious particles for at least 10 years.

The proportion of active and formed smokers in our series is similar to that of the general Spanish population (18%) but lower than the reported rate in other BE series, including Spanish and European registries (32,227,260).

Smoking prevalence varies significantly by region: in BE, current and former smokers make up 17% in China, 28% in India, 46% in Central, Northern, and Southern Europe, and 51% in Eastern Europe. In the Spanish registry, 8.3% were active smokers and 33% were former smokers, with an average consumption of 31 packs per year.

The exclusion of known COPD patients from our study may explain this difference.

In our clinic, BE patients with bronchial obstruction and a history of ≥10 pack-years are routinely diagnosed with BE+COPD, according to ROSE criteria. As a result, most patients with a significant smoking history were likely excluded from the study, given that a COPD diagnosis was an exclusion criterion.

However, in some cases, smoking history may not be recorded in our electronic medical records, or information on pack-years may be incomplete. The inclusion of smokers or former smokers in our study could therefore be attributed either to this missing pre-enrolment data or to the fact that COPD had already been clinically ruled out in those individuals. This could have skewed the results, with very few smokers in the study.

Smoking is the most important risk factor for COPD development in high-income countries. However, it is increasingly recognized as a contributor to BE development and progression(176). Smoking promotes inflammation and disrupts the balance of inflammatory molecules, promoting airway damage. It also alters the local immune response and impairs mucociliary clearance, increasing susceptibility to viral and bacterial infections. Moreover, smoking is a common risk factor for comorbidities, such as GERD, which can further negatively impact on BE symptoms and disease progression (176).The extent of exposure appears to play a significant role: the risk of developing BE is higher in individuals with a smoking history of more than 10 pack-years, particularly among younger individuals, females, and those who are overweight(261).

On the other hand, the COPDGene cohort provides valuable insights into the impact of BE on smoking-related damage (223). COPDGene is a multicenter initiative involving over 10,000 patients, aimed at studying the influence of genetic and environmental factors in the development of COPD. Data from this cohort suggest that BE itself may be a risk factor for heightened smoking-related harm: even among smokers with normal lung function, the presence of clinically significant BE was associated with a 15% increase in mortality (223).

6.3.3 CHRONIC RHINOSINUSITIS SYMPTOMS

UA symptoms were present in 40% of the cohort and were classified as chronic in two-thirds of these cases. Nasal symptoms, such as congestion, obstruction and blockage, were more commonly reported than ear or facial symptoms. Three patients were asymptomatic due to prior sinus surgery.

While the number of studies exploring the prevalence of CRS in BE patients has increased over the past fifteen years, there is limited information regarding UAS that do not necessarily fulfil EPOS criteria and lack CT or endoscopic correlation.

A 2018 study on BE patients (excluding subjects with PCD) reported UAS in 35% of the cohort, a prevalence closely matching that observed in our group. In that study, patients with UA involvement were characterized by an earlier onset of BE symptoms, higher rates of comorbid asthma, less extensive radiological involvement based on the Reiff score, and a lower prevalence of post-infective BE. These associations were not observed in our cohort(262). On the other hand, a study from 2009 described a much higher prevalence of chronic UAS in a BE cohort: anterior rhinorrhoea was reported by 89% of the sample, postnasal drip by 77% as well as nasal congestion, while sneezing by 59%. A combination of symptoms fulfilling the EPOS criteria was confirmed in 77% of the 88 patients enrolled in the study(263). Another series of BE patients from Turkey reported the presence of UAS in

at least half of the population, with nasal blockage in 50%, posterior rhinorrhoea in 42%, anterior rhinorrhoea in 35%, loss of smell in 34.5%, and sneezing in 28%. The study also found significant differences in the prevalence of some of these symptoms between BE patients with allergic rhinitis (AR) and the rest of the study population, which included individuals meeting EPOS criteria or with a previous diagnosis of CRS. In particular, patients with AR showed nearly double the prevalence of nasal blockage, anterior rhinorrhoea, loss of smell, and sneezing(264). It is important to take into consideration that the last two cohorts did not specify the exclusion or prevalence of PCD, whose presence could have impacted in the results. However, considering the lower prevalence of this condition in published series, it is assumable that if present, these patients would have been non statistically relevant. The findings of these studies suggest that individual symptom assessment may contribute not only to meeting diagnostic criteria for CRS, but also to the characterization of distinct CRS phenotypes. Moreover, UAS appear to vary over time. A population-based longitudinal study involving nearly 5,000 individuals found that only half of those initially meeting EPOS criteria for CRS had persistent symptoms at follow-up, representing just 4.8% of the total study population(265). In COPD, emerging evidence suggests that UAS may worsen over time, particularly in patients experiencing frequent exacerbations(266). Unfortunately, we do not have the same information regarding BE patients.

In conclusion, although upper airway symptoms are frequently investigated to rule out the presence of CRS, their role in the progression of patients with chronic respiratory diseases, including BE, remains poorly studied. Periodic assessment of these symptoms during follow-up could provide additional insights and may help identifying specific clinical phenotypes, even in patients who do not meet the diagnostic criteria for CRS. To date, no data are available about UAS symptoms evaluation over time in this subgroup.

6.4 QUALITY OF LIFE ASSESSMENT

An interesting finding of our analysis is the statistical correlation observed among all the qol questionnaires administered, despite each being designed to assess different clinical domains (cough, asthma-related symptoms, overall respiratory qol, and UAS-related qol). Moreover, this contrasts with the varying degrees of association with clinical severity markers and other clinical and instrumental variables. Only some qol scores showed a significant correlation with clinical severity outcomes, reinforcing the idea that perceived

quality of life is influenced by broader, possibly psychosocial or individual, factors beyond the measurable clinical presentation (Fig. 6.1).

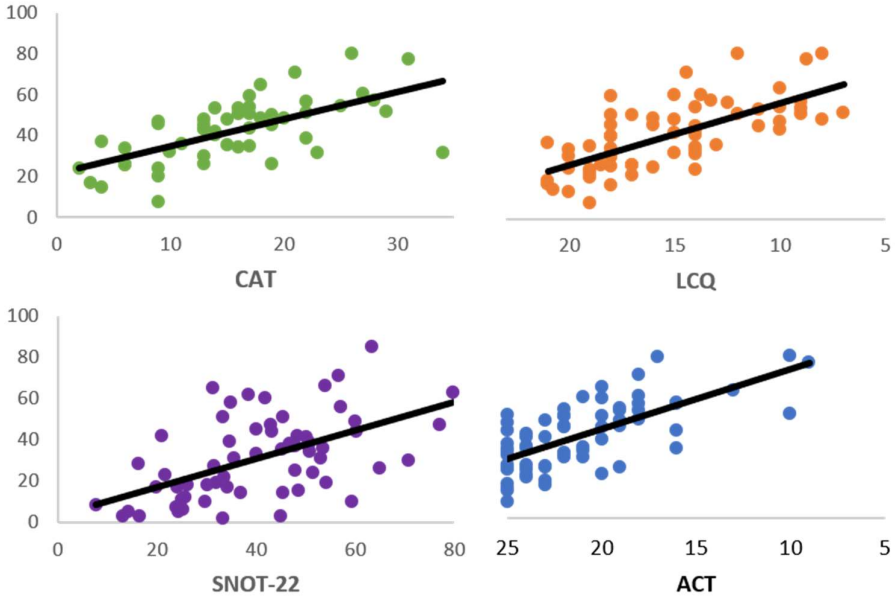


Figure 6. 1 Correlation between QoL scores. *Scatter plots showing the correlations between scores from various clinical questionnaires. Scores increase from left to right on the X-axis and from bottom to top on the Y-axis, corresponding to increasing symptom severity. The Y-axis represents the SGRQ.*
Abbreviations: LCQ: Leicester Cough Questionnaire, CAT: COPD Assessment Test, ACT: Asthma Control Test, SNOT-22: Sinonasal Outcome Test-22, SGRQ: St. George's Respiratory Questionnaire.

In our cohort, ***SGRQ*** results revealed a moderate overall quality of life impairment, with the highest burden reported in the symptoms' domain. While activity and impact scores were generally lower, a substantial proportion of patients (41.8%) reported significant symptom-related limitations.

The SGRQ is a validated tool for assessing quality of life in several respiratory diseases, including BE (267). It offers a comprehensive evaluation of disease impact across three domains: Symptoms, which reflect the frequency and severity of respiratory complaints; Activity, which assesses physical limitations related to dyspnoea; and Impact, which captures psychosocial effects such as social and occupational restrictions, health-related concerns, daily life interference, embarrassment, and stigma. While highly informative and valuable in research settings, its length and completion time (10–15 minutes) make it le**ss practical for routine clinical use.**

The mean SGRQ score in our cohort is consistent with findings from previous studies (268,269). Interestingly, although patients reported high symptom scores, indicating a

persistent and burdensome respiratory symptomatology, these symptoms appeared to have a more limited impact on daily activities and psychosocial well-being. This pattern may reflect a degree of resilience or empowerment in patients with a long history of bronchiectasis, who may have adapted over time to the chronic nature of their symptoms and the lifestyle changes imposed by the disease. Notably, women in our study reported significantly higher scores in the Impact domain, suggesting a greater perceived disruption of daily life. This difference may be influenced more by emotional or psychological factors than by physical limitations, as no significant differences were observed in the Activity domain.

Previous studies have shown that total SGRQ scores correlate with several clinical variables, including dyspnoea, sputum production, frequency of exacerbations, and lung function parameters (FEV1, FVC%). Some symptoms may be more closely associated with specific subscales: for example, a Spanish study found that wheezing correlated only with the Symptoms domain(269).

In our cohort, correlation was confirmed for exacerbations, dyspnoea, and FEV1 litres but not percent predicted value. This last finding suggests that factors such as age and sex, already adjusted for in predicted reference equations, may still affect patients' perception of quality of life. Therefore, absolute reductions in lung function might lead to a greater perceived decline in health status than indicated by normalized percent predicted values, which tend to minimize inter-individual variability. On the other hand, the association of SGRQ with other variables was not observed in our subjects, possibly due to the small size of the sample and the non homogeneous distribution of severity in the cohort.

The ***ACT*** was administered to all patients to evaluate whether our diagnostic criteria effectively identify individuals with differing asthma-related quality of life. Specifically, we aimed to explore potential associations between the clinical parameters assessed in our study and patients' symptom burden as reflected by ACT scores. Although not validated for use in bronchiectasis, the ACT is a questionnaire specifically designed to assess disease control in asthmatic patients.

In this study, it was used to estimate the presence and severity of asthma-like symptoms and to investigate their relationship with a confirmed asthma diagnosis in our cohort.

Most patients reported good overall asthma-like symptom control based on ACT scores, with lower scores observed specifically for morning symptoms and the use of reliever inhalers. Given the ACT's specificity for asthma, no comparative data are available from bronchiectasis cohorts without asthma, limiting direct comparisons with similar populations.

For the same reason, the absence of significant correlations with all descriptors in our cohort, including severity, is not unexpected, and supports the idea that disease-specific instruments may not be able to predict clinical severity when applied to other conditions, despite the presence of shared features.

Similarly to SGRQ, ***CAT***, scores in our cohort indicated a predominance of moderate symptoms, with only a minority of patients (n=12) reporting high or very high impact. Among individual items, cough, sputum production, and exertional dyspnoea emerged as the most burdensome symptoms, reflecting the typical clinical profile of bronchiectasis.

Although originally developed to assess quality of life in COPD, the CAT has since been validated in other respiratory diseases, including bronchiectasis, showing good psychometric properties (270–272). Given its broad applicability and validation across chronic respiratory diseases beyond COPD, a revised version of the questionnaire, renamed “the Chronic Airways Assessment Test (CAAT)”, has recently been proposed (273). The main modification lies in the wording of the questions, which now refer to “chronic respiratory diseases” rather than COPD specifically. This updated version has been validated in patients with COPD and asthma, but not yet in BE (273). For this reason, we used the original CAT in our study.

In BE, CAT has demonstrated good correlation with disease severity, such as BSI and E-FACED scores, as well as with dyspnoea and exercise limitation measured by tests like 6 minutes walking test (6MWT) and cardiopulmonary exercise testing (CPET) (270,271).

In our study, correlations between CAT scores and clinical variables mirrored those observed for the SGRQ (FEV1 in litres, exacerbations, and dyspnoea), and statistical correlation between the two scores was confirmed. These data support the potential of this tool as a valid alternative to more complex questionnaires, particularly in clinical practice. Its ease of use, clarity, and rapid completion time, combined with its good correlation with bronchiectasis-specific instruments such as the SGRQ, make it well-suited for both research settings and routine outpatient assessments.

Regarding *upper airway symptoms*, their overall impact appeared to be moderate in most patients, consistent with the profile of classical BE symptoms evaluated through the other instruments. The mean total *SNOT-22 score* was moderate (31.5, SD 19.8). Nearly half of the patients reported a moderate burden from sinonasal symptoms, while 17% experienced a severe impact. Nasal symptoms had a slightly higher impact than ear or facial symptoms. Although total SNOT-22 scores did not differ significantly between groups, psychological impact scores were notably higher in female patients.

SNOT-22 is a quality-of-life questionnaire validated for patients with CRS, quantifying UAS and their impact in different aspect of patients' life. As per ACT and CAT, we administrated the questionnaire to all our cohort, regardless of CRS diagnosis. Differences between patients with and without CRS in our cohort will be discussed in chapter 6.11.

Despite including BE patients both with and without UAS, the mean SNOT-22 score in our cohort was comparable to those reported in studies focusing exclusively on BE patients with CRS. For instance, Lee et al. observed a mean score of 37 points, indicating a moderate impact of UAS in a CRS-defined BE population. In their study, SNOT-22 scores showed significant correlations with cough-related quality of life (measured by the LCQ), general quality of life (assessed via the Bronchiectasis QoL questionnaire), as well as with disease severity and radiological extent of bronchiectasis(274).

In the patients included in our study these correlations were only partially confirmed, as SNOT-22 correlated with LCQ, CAT and SGQR, but not with severity scores or Reiff index.

On the other hand, the mean SNOT-22 score in our BE population was significantly higher than the average reported in the literature for a healthy control group, which is approximately 11 points (275). Even after excluding all patients who reported at least one UAS in the symptom questionnaire, the mean score in our cohort remained elevated, at 23 points.

This finding may suggest that BE patients are accustomed to sinonasal symptoms and may not perceive them as clinically relevant, even though these symptoms can still negatively affect their quality of life. Additionally, it is possible that responses to some SNOT-22 items, particularly those not directly related to upper airway symptoms, such as sleep disturbance, cough, or psychological distress, are influenced by lower airway issues. Patients may have difficulty distinguishing between upper and lower airway symptomatology when completing the questionnaire.

SNOT-22 scores showed significant differences between male and female subjects. As observed with the SGRQ, no significant differences were found in symptom-related domains (rhinologic, extra-nasal, and ear/facial symptoms), whereas women reported significantly higher scores in domains assessing psychological impact and quality of life. This may suggest that, in female patients, the same clinical condition is perceived as more burdensome, or alternatively, that male patients tend to underreport or underestimate the psychological consequences of their symptoms.

6.5 FUNCTIONAL ASSESSMENT

The functional assessment included spirometry with PBD, DLCO, and plethysmography for lung volume evaluation. Overall, mean values for FEV1, FVC, and FEV1/FVC in our population were within normal limits. However, only one-third of the sample exhibited normal lung function, volumes, and CO diffusion, while the remaining subjects demonstrated at least one alteration in LFTs.

An obstructive pattern was observed in one-third of the cohort, with half of these patients also showing air trapping. DLCO impairment was relatively uncommon.

Additionally, more than 15% of patients exhibited air trapping without obstruction.

PBD was positive in only four patients. Post-BD FEV1 values were consistent with those of the normal population, while pre-BD values were significantly lower. Bronchial obstruction was identified in just one patient, and it did not resolve after BD. Two patients exhibited air trapping.

The restrictive pattern was less frequent, present in approximately 10% of the cohort. Most of these individuals had normal DLCO values and lung volumes. Only three patients presented with a mixed pattern, while other combinations of DLCO and plethysmography abnormalities were rare.

DLCO values were reduced in more than half of the cohort, but only 10% presented reduced levels of KCO.

Improved longitudinal spirometric data, available for a subgroup of 49 patients, revealed non-significant median reduction of 50ml (2.1%) in 12 months. Approximately 10% of patients exhibited a variability greater than 20% between tests. According to the literature, healthy subjects exhibit a physiological decline of approximately 20 to 45 ml/year, with a faster rate observed in males (276). Data on BE patients are limited, but the available findings appear to not very different from those reported for healthy individuals(277,278). Our cohort appears to exhibit a slightly faster decline, possibly due to the high prevalence of aetiologies typically associated with more severe disease, accelerated progression, and greater intra-individual variability in lung function, particularly PCD(279,280).

On the other hand, other lung function data in our cohort aligns well with previously published findings, particularly from the EMBARC and RIBRON registries. The mean FEV_1 reported in the European EMBARC registry was 1.78 L (76.9%), and 1.86 L (73.9%) in the Spanish RIBRON cohort. Corresponding FVC values were 2.65 L (91.4%) and 2.66 L

(83.8%), respectively. Additionally, the RIBRON registry provided data on static lung volumes and diffusion capacity for a subset of patients, reporting a mean residual volume (RV) of 138% and a DLCO of 81%. These international cohorts presented slightly higher levels of airflow obstruction compared to our patients, with an obstruction prevalence of 35% in EMBARC and 53.1% in RIBRON(32,227).

Although spirometry is the most widely used instrumental test for the follow-up of BE, few studies have comprehensively described lung function in this patient population, leaving it relatively understudied.

The relatively limited attention given to functional physiopathology in BE, compared to other aspects of the disease, is likely due to the unclear prognostic value of spirometry in this context. Existing data suggest that the evolution of lung function is independent of dyspnea, exacerbation frequency, and the extent of bronchial damage observed on HRCT (281). Some authors have reported a correlation between FEV1 levels and disease severity only in patients with advanced impairment (FEV1 < 50%), particularly in those chronically infected with PA (282–284). Also, lung function has been shown to be a poor predictor of postoperative complications in lung resection in BE patients (285)).

This pattern is similar to CF, the condition that has historically served as the primary model for both BE management and research. In CF, it has been well established that lung function values hold limited value in the early and moderate stages of disease, as spirometric decline typically follows the onset of structural damage and becomes apparent only in more advanced stages (286).

The most thorough analysis of lung function to date was conducted by Radovanovic et al. in 2018, involving nearly 200 BE patients. Their study evaluated a wide range of pulmonary function parameters, including static and dynamic volumes, DLCO, FEV1, and RV reversibility. While 60% of patients had normal spirometric values, only 10% had a completely normal LFT(132). This trend is mirrored in our data and suggests that spirometry alone may be insufficient to fully assess the functional status in BE patients.

Interestingly, air trapping impairment was more prevalent in the Radovanovic cohort (70%), possibly reflecting differences in patient characteristics, particularly a higher rate of smoking exposure (42% vs. 20%) and a greater proportion of severe cases (30% vs. 20%)(132). The prevalence of obstruction was also higher in Radovanovic cohort than in ours, aligning closely with the EMBARC cohort (41%)(227).

The exclusion of patients with known COPD from our study is likely a key factor contributing to the lower prevalence of obstructive patterns in our cohort, as this comorbidity is associated with more severe lung function impairment (121).

On the other hand, the rate of restrictive pattern observed in our cohort was slightly higher than the one reported by Radovanovic (5,5%). Restrictive pattern is the less described in BE, however, seems to have great impact in mortality. Loebinger and colleagues assessed factors influencing mortality in a cohort of 91 patients followed for 14 years. In their study, high RV/TLC, low TLC and low DLCO were associated with higher mortality, suggesting an important role for restrictive component (287). Restriction in BE can be secondary to alterations like parenchymal scarring due to previous infection, peribronchial fibrosis and pleural disease (288,289).

An increase in RV was observed in approximately half of our patients, including those with normal spirometry, a finding not far from the 70% reported by the Monza-Milan cohort(132). An elevated RV is considered a marker of premature airway closure and air trapping (288,290), and has been linked to distal airway inflammation in COPD (291). In a study performed in patients without known respiratory diseases at the enrolment, the presence of isolated RV elevation was correlated to the diagnosis of BE during the study in 31% of the sample (compared with the 8% of diagnosis in patients with normal lung function), and with mucus plugging and bronchial wall thickening in 46% of the subjects (292).

The presence of elevated RV generally reflects dysfunction of the small airways. Therefore, observing this finding in BE patients without other concomitant airway diseases may appear surprising, as BE is typically considered a disease predominantly affecting the large airways. However, a role of the small airways in its pathogenesis has been proposed since the 1950s through anatomopathological studies (293). In recent years attention to the small airways has intensified, and the mechanisms through which they contribute to BE development have begun to be partially elucidated (294). In BE, the upregulation of mucin production in the small airways appears to lead to mucus hyperconcentration, resulting in hypoxia in the distal airways. These conditions starting in the distant small airways contribute to the vicious cycle of mucus stagnation, inflammation, and remodelling, which ultimately leads to structural damage, and could be functionally reflected by the increment of RV (295,296).

However, the significance of RV and air trapping in the clinical course of BE remains poorly documented. Lopes and colleagues found that in a cohort of BE patients (which included CF cases), the mean RV was above reference levels. However, when comparing BE

aetiologies, only patients with CF and PCD showed significantly higher RV levels, while those with BE due to TB, NTM, and rheumatoid arthritis (RA) had normal plethysmography values (297). This finding had already been described in PCD patients, correlated with HRCT findings such as air trapping, BE extension and presence of atelectasis(297). Notably, Radovanovic observed high rates of RV reversibility following bronchodilator administration, a finding more common than FEV1 reversibility, suggesting a role of small airway dysfunction in BE pathophysiology and response to treatment.

Consistently with other series, DLCO in our study was below 80% in more than half of the patients. Previous studies in BE patients have shown a correlation between reduced DLCO levels and clinical variables such as BMI, hospitalization rate, exacerbations, cardiorespiratory comorbidities (COPD, ILD, pulmonary hypertension (PH)), and the radiological extent of BE (284,298). Additionally, accelerated DLCO decline over time has been observed in BE patients (299). Several mechanisms have been proposed to explain DLCO impairment in BE. Chronic bronchial inflammation and mucus plugging could contribute to ventilation inhomogeneity, reducing diffusion capacity, particularly in patients with more extensive BE (284). As with other chronic respiratory diseases, reduced DLCO could be associated with the presence of emphysema; however, other studies have reported a low prevalence of emphysema on CT scans, which is insufficient to account for the observed DLCO reduction, as it happens in our cohort (287). More likely, vascular changes play a significant role in DLCO impairment. As said, PH can be correlated with DLCO impairment in BE; the presence of PH has been linked to increased number of lobes affected and with cystic BE, as well as it happens for DLCO (300,301). Although PH appears to be a common complication in BE, affecting up to 33% of patients according to available data (302,303), its true prevalence remains unclear, as limited evidences are available on BE patient. Most studies have been monocentric and often focus on patients with established PH, rather than screening all BE patients. Nevertheless, it is likely that PH plays a more significant role in BE than traditionally thought, potentially contributing to DLCO reduction, especially in advanced disease stages (287). On the other hand, the smaller proportion of patients with reduced KCO may suggest the presence of non-homogeneous ventilation secondary to airway remodelling. The significance of KCO in relation to DLCO has been debated across various airway and lung conditions, with inconsistent findings reported in the literature(304,305). To date, the role of KCO in bronchiectasis has not been specifically investigated.

Regarding PBD test results, only a few studies have specifically focused on this aspect in patients with BE. Earlier data reported unexpectedly high rates of PBD positivity, with up to

34% of patients showing a response (306). In contrast, more recent studies have observed bronchodilator hyperresponsiveness in approximately 7–8% of BE patients, figures that are more consistent with, though still slightly higher than, the 5% observed in our cohort (132,144,307). However, we applied the updated GINA 2022 criteria to define a positive response (an increase in FEV1 of more than 10% of the predicted value) rather than the earlier 1991 ATS/ERS definition, which required both an increase of at least 12% and an absolute gain of more than 200 mL in FEV1. The older definition has been associated with a higher risk of overdiagnosing airway hyperresponsiveness, an issue addressed by the revised criteria, which aims to improve specificity and reduce false positives. Applying the ATS/ERS 1991 definition to our cohort, positivity rises to 10.4%, in line with other authors. In their series, Guan and colleagues reported a PBD positivity rate of 7%. In their study, baseline FEV1 and FVC levels of patients with hyperreactivity were lower compared to the rest of the cohort, although no accelerated decline over time was observed. Interestingly, the response to PBD was not associated with blood or sputum eosinophilia, but there was a trend toward a higher prevalence of PA, suggesting a possible role of chronic infection in the expression of airway hyperreactivity (307).

PBD change is typically considered a marker of intrinsic bronchial hyperresponsiveness. However, during our study, we observed that many patients experienced spontaneous expectoration and auscultatory changes immediately after performing the pre-BD spirometry manoeuvres. These modifications may be due to the nature of spirometry itself rather than to a response to the bronchodilator. In fact, spirometry performance requires forced expiration with an open epiglottis and prolonged exhalation, movements that closely mimic those used during airway clearance techniques.

In a study on CF patients, FEV1 and FVC changed significantly (5 to 42%) following airway clearance(308). In BE patients, the effect of mucus mobilization and reduction in thoracic pressure through forced manoeuvres similar to spirometry has not been formally assessed, but it could contribute to subthreshold PBD variation or influence PBD response during acute infection.

In conclusion, although mean spirometric values were within normal limits and most patients showed no evident impairment, the inclusion of full lung function testing revealed a substantially higher prevalence of abnormalities not detectable by forced spirometry alone. While body plethysmography and DLCO are not routinely performed in the follow-up of bronchiectasis, current evidence suggests that these tests may serve as early indicators of disease severity, progression, and poorer prognosis. Nonetheless, further studies are needed to clarify the underlying mechanisms beyond bronchial dilation that

contribute to these alterations. Positive PBD was infrequent in our cohort, while subthreshold changes following spirometry may reflect mucus mobilization rather than true reversibility, warranting cautious interpretation of borderline responses.

6.6 INFLAMMATION AND ALLERGY

Mild leucocytosis was present in 13% of patients tested, while almost one quarter presented CRP levels above normal range.

Peripheral eosinophilia was observed in 16% of patients, for all of them specific causes of eosinophilia were discarded; on the other hand, neutrophils were elevated in 10% of the cohort.

Elevation of CRP and neutrophilia did not show any significant correlation with variables such as presence of CBI or sputum production.

Among 74 patients were FeNO was recorded, 25% had levels >25ppb, while most of our patients had normal levels of IgE, while were significantly elevated only in 5 patients (>300 µL).

20% of subjects had positive Phadiatop. Among them, 5 had IgE > 150 µL. No correlation was encountered with FeNO levels or eosinophilia.

The role of Type 2 inflammation in bronchiectasis has received growing attention in recent years; however, available data remain limited and often contradictory.

Eosinophils, once considered uninfluential in BE, are now recognized as the predominant inflammatory cell type in approximately 20% of patients, representing the so-called “eosinophilic endotype.” Although this definition refers primarily to elevated eosinophil levels in the airways, peripheral eosinophilia is commonly accepted as a reliable surrogate, given the demonstrated correlation between peripheral and airway eosinophil counts(309).

Peripheral eosinophilia has been associated with increased disease severity, lower lung function, worse quality of life, and shorter time to exacerbation (309,310). Notably, even eosinophil counts below 50 cells/µL have been linked to more severe disease, suggesting that normal eosinophil levels may play a protective role in BE (311).

As seen in other respiratory diseases, particularly COPD (312), peripheral eosinophilia also appears to be a useful predictor of ICS responsiveness in BE (313).

In our study, eosinophil levels did not confirm these associations, particularly regarding severity, lung function, exacerbation frequency, and QoL and our limited sample size could

play a significant role. However, patients with elevated eosinophils exhibited distinct clinical features, including reduced sputum purulence and a lower prevalence of CBI, suggesting a phenotypic correspondence of the eosinophilic endotype.

On the other hand, the absence of correlation between lung function and blood eosinophilia or neutrophilia suggests that lung function may not be a reliable indicator of the predominant inflammatory pattern in patients with BE.

The potential of FeNO as a biomarker in patients with BE has also been explored, with great variability in results.

Some studies report higher FeNO levels in bronchiectasis patients compared to healthy controls, although still lower than those typically observed in asthma or COPD. In these cases, FeNO was associated with greater disease severity, but not with the presence of exacerbation (314,315). In contrast, a more recent study involving patients hospitalized for exacerbations of bronchiectasis, COPD, or both, found increased FeNO at admission, which decreased at discharge (316).

Conflicting results may be influenced by unaccounted confounding factors. For example, a higher prevalence of undiagnosed patients with PCD, characterized by impaired airway NO production and more severe disease, may significantly impact FeNO measurements.

On the other hand, the presence of *PA* has been associated with lower FeNO levels (317). Considering that patients with *PA* CBI tend to have more severe disease and more frequent exacerbations, factors typically associated with increased FeNO levels as previously pointed out, these finding further complicate the interpretation of FeNO as a biomarker in bronchiectasis. Interestingly, levels of FeNO do not seem to be influenced by the use of ICS in BE patients, suggesting a possibly low correlation with the extent of airways inflammation in these patients(317).

In our cohort, FeNO did not correlate with disease severity, CBI, or *PA* CBI. These findings may have been influenced by factors such as the underlying aetiology, particularly the high proportion of patients with PCD, the elevated prevalence of *PA* CBI, and the limited sample size, all of which may have significantly impacted the results. On the other hand, lower levels of FeNO correlated with the presence of BE in a higher number of pulmonary lobes. The clinical and physiopathological significance of this association is not clear and should be confirmed in a higher number of patients.

Although total IgE is routinely measured in BE patients to help exclude ABPA, its clinical relevance in BE patients without ABPA has been rarely explored. A study by Chen et al.

reported that patients with IgE levels above 60 kU/L had a greater number of lobes involved compared to those with lower levels. However, this threshold appears low compared to commonly accepted reference values; in our laboratory, for instance, the upper limit of normal is 150 kU/L. In our cohort, most patients had IgE levels within this normal range, which limited the ability to detect any significant correlations with clinical parameters, including radiological findings. Our findings closely align with those from the EMBARC "non-asthma group," in which IgE levels were ≤150 kU/L in 85% of patients, 150–300 kU/L in 7%, and >300 kU/L in the remaining 8%. This contrasts with the "asthma" subgroup, where only 66% of patients had IgE levels within the normal range(122). However, the interpretation of EMBARC's IgE data requires caution. These values were available for only a limited subset of patients and may be biased, as IgE testing was likely performed more often in individuals with suspected asthma or features of Type-2 inflammation(122). Furthermore, data on IgE distribution in the overall EMBARC cohort have not been reported, which further limits the generalizability of these findings.

Most of our patients with elevate IgE levels also presented positive Phadiatop.

Phadiatop is a sensitive and specific method to assess allergies(318). One of the main advantages, compared with skin prick tests, is the rapid execution that does not require the use of human resources and time, and can be included in a rutinary blood analysis, especially for screening purposes as in our study.

The role of allergies in BE remains a largely understudied aspect of the disease. A recent study by Zhang and colleagues demonstrated that, in addition to asthma and CRS, other allergic conditions such as allergic rhinitis and atopic dermatitis are also associated with the development of BE(319). The authors identified several metabolic and immune pathways that showed significant statistical correlations with this association. These mechanisms may contribute to the pathogenesis of BE and warrant further investigation in dedicated studies(319).

Considering Type 2 inflammatory markers altogether, in our cohort only peripheral levels of eosinophils showed correlation with the other biomarkers, FeNO and IgE, while no association was observed between these two variables.

This is not dissimilar from what has been described in literature: a recent study on 145 patients with bronchiectasis (excluding those with asthma) showed different combinations of Type 2 biomarkers. These combinations were associated with varying risk profiles for exacerbation and disease severity. Notably, patients with low blood eosinophils and high FeNO had a reduced risk of exacerbation compared to those with other biomarker

combinations(320). These findings suggest that Type 2 inflammation in bronchiectasis may be regulated by complex, not yet fully understood mechanisms, and that meaningful clinical interpretation likely requires a combined biomarker approach rather than reliance on a single parameter.

6.7 MICROBIOLOGY ASSESSMENT:

Microbiological analysis revealed a high rate of pathogen isolation from sputum samples collected either during visit one or in the previous year, with PA emerging as the most frequently detected organism. Chronic *PA* infection was confirmed in a significant proportion of patients, being present since several years in most patients and frequently associated with the mucoid phenotype. A subset of patients was considered with *PA*-CBI despite recent negative cultures, due to previous failed eradication attempts followed by intermittent sputum positivity, and/or ongoing inhaled antibiotic therapy. Besides *PA*, other chronic infections were also identified, particularly those caused by *H. influenzae* and *S. aureus*, with many patients showing evidence of polymicrobial CBI. These findings underscore the complex nature of airway microbiology in the study population.

Infection plays a central role in the pathogenesis and clinical trajectory of BE, where impaired immune clearance fosters persistent microbial colonization and chronic airway inflammation (321–323). The presence of CBI is well-established as a marker of disease severity, poor QoL, and increased mortality (173,287,324), and this impact is reflected in its incorporation into most BE severity scores (325). Consistent with previous studies, including the Spanish RIBRON registry, our cohort showed a high prevalence of bacterial isolation, most commonly *PA*, *H. influenzae*, and *S. aureus,* despite the absence of acute symptoms at the time of sputum collection (227,326). Notably, fungal isolation in our study was significantly more frequent than reported in RIBRON, where *C. albicans* and *Aspergillus spp*. were detected in only 2.4% and 0.9% of patients, respectively. This discrepancy may reflect the more systematic use of fungal cultures in our centre, where all samples undergo routine testing for bacteria, mycobacteria, and fungi. While prior studies have suggested an association between chronic antibiotic or ICS use and increased fungal colonization (327,328), our sample size limited the statistical power to confirm this. Patients treated with nebulized antibiotics in our cohort appeared to exhibit a higher frequency of *Aspergillus* isolation (3/15 of those on inhaled antibiotics vs 2/54 in those not on inhaled antibiotics). However, due to the very limited number of patients with *Aspergillus* isolation, these findings should be interpreted with caution and do not allow for definitive conclusions. As in other cohorts, most cases of positive culture met criteria for CBI, with pathogen

distribution again dominated by *PA*, followed by *H. influenzae* and *S. aureus*, aligning with current literature (32,227,326).

Considering the clinical and pathogenic relevance of *PA* in BE, we performed a separate analysis on patients with CBI sustained by this microorganism. *PA* not only represents the most common cause of CBI in adult BE populations from country but also plays a direct role in driving the disease's pathogenesis and clinical manifestations(321). Through the release of a wide array of virulence factors, PA disrupts host immune responses, diminishes antimicrobial activity, and promotes both local and systemic inflammation. Additionally, it contributes to epithelial damage, impairs repair mechanisms, and reduces mucociliary clearance, thereby sustaining the "vicious vortex" that characterizes BE progression (28,321). Clinically, this is reflected in increased symptom burden, worse QoL, higher exacerbation frequency, accelerated functional decline, and reduced survival (283,329,330).

Overall, the microbiological profile observed in our patients was consistent with previously published series and identified a more severe population with a higher symptom burden.

6.8 RADIOLOGICAL CHARACTERIZATION

Radiological severity was assessed through Reiff score.

More than 60% of patients presented mild bronchiectasis (Reiff 1-6); while 34% had moderate BE (Reiff 7-12), and only 2 subjects (2,6%) showed a severe disease extension (Reiff ≥13 points).

Lower lobes had higher presence of BE compared with middle and superior lobes. On the other hand, distribution was comparable between left and right lobes.

Cystic bronchiectasis interested 15 patients, and in half of the cases (7/15) were observed in lower lobes.

Other radiological alterations were observed with different frequency: emphysema was rare, being present only in 2 patients. BWT interested more than 85% of the cohort, while MP the 67%. GGO was present in 43% of the subjects, and was centrilobular in two thirds of them, indicating infection. Air trapping interested almost 90% of those with availability of expiratory scan and 70% of the entire cohort.

Imaging plays a crucial role in the evaluation of BE, as the condition is primarily diagnosed through radiological methods, and CT scans are essential for confirming bronchial

dilatation, an essential feature in diagnosing the disease. Beyond assessing bronchial diameter, CT scans provide additional valuable insights. However, the full significance of these findings, as well as their relationship with airways comorbidities or LFT abnormalities, has not fully described yet.

In our cohort, severity of BE extension according to Reiff index was slightly higher than reported in the European database, despite lower overall BSI score(227). The median Reiff score was 5 points (IQR 3-8), compared to 3 (IQR 2-4) in the overall EMBARC cohort and 4 (IQR 2-6) in Southern Europe(227). In contrast, the prevalence of cystic BE was consistent with previously published data from both Spanish studies and the EMBARC database for Southern Europe (32,227). Consistent with earlier findings, Reiff scores were significantly correlated with BSI and FACED scores (32,227,331). This is partly expected, as radiological extension is one of the variables included in both scores. However, since Reiff is purely radiological while BSI and FACED are multidimensional, this correlation suggests that the Reiff score may reflect not only the anatomical extent of bronchiectasis, but also its clinical impact. This supports the idea that Reiff may offer a more informative assessment of radiological severity than simply counting the number of affected lobes.

Interestingly, Reiff scores also showed a negative correlation with FEV1 values, in contrast to the findings of other authors(331), and also with FVC and TLC. This finding may suggest that increased bronchial distortion, described by the Reiff score, contributes to a tendency toward restrictive ventilatory changes. In fact, areas with more severe bronchial alterations likely exhibit reduced ventilation efficiency and contribute to an increase in functional dead space. Conversely, this structural distortion may not necessarily lead to airway obstruction, which could explain the lack of correlation with FEV1/FVC ratios.

The segmental distribution of BE in our cohort was consistent with findings from Spanish patients in the RIBRON registry, that showed a higher prevalence of BE observed in the lower lobes, middle lobe, and lingula compared to the upper lobes(32).

The distribution of BE is strongly influenced by the underlying aetiology of the disease, and some authors have suggested that this factor could guide the etiological investigation of BE. Both the distribution pattern, focal or diffuse, and the lobar localization (lower lobes, middle lobe, or upper lobes) may depend on specific underlying conditions. Focal BE is typically associated with localized damage mechanisms, such as foreign body aspiration, anatomical anomalies like congenital bronchial atresia, acquired bronchial stenosis secondary to infection or inflammatory diseases, prolonged intubation, or extraluminal compression, mainly related to lymphadenopathies or mediastinal masses(332). On the other hand,

diffuse BE is usually secondary to systemic diseases, which can affect different pulmonary segments in varying ways. The upper lobes are most commonly involved in BE associated with ABPA, TB, sarcoidosis, or damage following radiotherapy(332,333). NTM disease typically affects the middle lobe and lingula. In contrast, the lower lobes are the primary sites of BE related to aspiration and GERD, childhood infections, PCD and PID (333,334). However, this classification represents a simplification and should be viewed as a conceptual model rather than a strict rule.

Other radiological findings, beyond bronchial dilatation, have also been correlated with disease severity and specific aetiologies. The evaluation of radiological alterations not typically included in BE assessment in our cohort has yielded interesting results.

The presence of emphysema is not uncommon in BE patients and has been linked to disease severity and mortality (335,336). Its importance is underscored by its inclusion as a variable in the BRICS score, a scoring system used to stratify BE patients based on radiological characteristics(337). In the score's validation study, Bedi and colleagues observed a correlation not only with radiological and overall severity scores (Reiff, Bhalla, BSI, FACED), but also with elevated levels of sputum NE(337). Previous research has highlighted the matrix degradation properties of NE, which can lead to parenchymal damage(338). This mechanism may help explain the higher prevalence of emphysema in BE patients with active neutrophilic inflammation(337).

In our cohort, the overall presence of *emphysema* was assessed, revealing a very low prevalence. No segmental distinction was made, which prevented the calculation of the BRICS score.

On the other hand, MP, BTW and GGO were common findings in our patients.

While most studies focusing on these findings are small or consider only a single alteration, a comprehensive paper by Pieters and colleagues previously detailed these radiological findings in depth(339). They analysed over 500 CT scans from BE patients using the Bronchiectasis Scoring Technique for CT (BEST-CT), which evaluates the percentage of lung volume affected by various alterations, including atelectasis/consolidation, BE with and without MP, BWT, MP alone, GGOs, and bullae(339).

In their cohort, *MP* was the most common finding, observed in 87% of scans, and associated with BE in 74%. It also showed a significant correlation with FEV1 (339). This association was confirmed in our cohort, where patients with MP also presented with more extensive BE. Our results are consistent with both proposed pathogenic mechanisms and previous

literature. The combination of BE and MP may indicate long-standing inflammation that led to structural airway changes, along with ongoing disease activity, as suggested by the presence of MP(339).

Indeed, mucus stagnation plays a central role in both the initiation and perpetuation of the vicious vortex that underlies BE pathogenesis, sustaining a local proinflammatory environment (323). In line with this, BE extension and the presence of MP have been identified as the main radiological risk factors for progression to clinically significant BE in a population of asymptomatic patients over a 3-year follow-up (340).

The mechanisms driving mucus hyperproduction in BE are classically attributed to impaired mucociliary clearance, mucus dehydration, neutrophilic inflammation, and chronic infection(323). However, in some patients MP formation could also follow an alternative pathway driven by Th2 inflammation. This has been well documented in asthma, where MP is emerging as a potential target for biologic therapies in Th2-high phenotypes (341–343). Similarly, in BE patients, Ren and colleagues observed higher frequency of MP and increased extension of BE in patients with elevated levels of IgE, peripheral blood eosinophils, and FeNO(344). These findings suggest that while BE and bronchial remodelling may represent a common endpoint, the presence of mucus in BE airways could arise through different pathogenic pathways, potentially requiring different management strategies. Likely, the development of advanced tools such as volatile compounds analysis or radiomics and AI-based software for CT interpretation could aid in distinguishing between different types of airway secretions, helping clinicians identify the most appropriate therapeutic approach.

In Pieters' cohort, *BWT* was less frequent compared to ours (58%). BWT is a classical radiological alteration, potentially reversible, typically observed in various conditions, including BE, asthma, and COPD. However, it has also been described as an incidental finding in healthy subjects (345–347). BWT is generally considered a radiological marker of airway inflammation. As expected, its presence has been associated with reductions in FEV1 and FEF25-75, an obstructive functional pattern, increased frequency of exacerbations, presence of wheezing, and impaired QoL (348,349). Moreover, BWT has been correlated with increased airway resistance in BE, which may contribute to the progressive worsening of airflow obstruction observed in LFTs(350). In our cohort, the correlation of BWT with worse lung function is confirmed. Additionally, the association with greater radiological extension expressed by Reiff values and higher number of lobes with might be indicative of the bidirectional relationship between chronic inflammation and radiological damage: persistent inflammation leads to airway remodelling and dilatation,

while in presence of greater extent of bronchiectasis there is increased risk of exacerbations, chronic infection and overall disease severity, all risk factor for inflammation persistence. Unfortunately, as with emphysema and MP, manual quantification of BWT is extremely time-consuming, and was not performed in our study. Moreover, BWT quantification is subject to inter-observer variability that could bias the results. To address this limitations, new automated methods for BWT measurement are being developed(351). This is particularly relevant in BE, where the presence of BWT can affect the accurate identification of bronchial dilatation, potentially leading to over- or underdiagnosis, especially in cases with a marked discrepancy between the inner and outer bronchial diameters(352).

Regarding GGO, its prevalence in our study (43%) was comparable to that reported by Pieters and collaborators (34%). GGO is defined as increased pulmonary opacity with preservation of bronchial and vascular margins (353). It results from partial filling of the alveolar spaces, thickening of the interstitium or alveolar walls, or a combination of these processes (354). GGO may occur secondary to a wide range of respiratory conditions, including pneumonia (infectious and non-infectious, such as organizing pneumonia or hypersensitivity pneumonitis), vascular disease (e.g., acute pulmonary oedema), and interstitial lung diseases. When GGO involves only centrilobular structures, such as small pulmonary arteries, bronchioles, lobular lymphatics, or connective tissue, it is referred to as centrilobular GGO, which is more commonly associated with infections and bronchiolitis (354). Although GGO is frequently reported as a radiological feature in BE, its clinical significance and role have been only marginally explored. Higher prevalence has been noted in certain subgroups, such as patients with NTM infection (355) or PCD (356). In our cohort, patients with GGO showed greater radiological extension of BE and a higher prevalence of BWT. Its presence, similarly to BWT, may therefore indicate increased inflammation contributing to or resulting from bronchial damage. This interpretation is consistent with existing literature: when reported, GGO is usually considered an inflammatory sign in combination with other findings. In BEST-CT, the combined sub-scores of MP, BWT, and GGO, along with atelectasis/consolidation (not assessed in our study), contribute to a composite outcome that reflects radiological evidence of inflammation. In the EMBARC CT study, radiological markers of inflammation were correlated with the frequency of hospitalization, reflecting heightened disease activity that predisposes to acute infections and contributes to increased radiological sequelae (339).

Finally, our subject showed very high prevalence of air trapping.

During the expiratory phase of CT scans in healthy individuals, a homogeneous increase in lung attenuation is typically observed. In contrast, areas of air trapping are characterized by patchy or diffuse regions of preserved lung attenuation. This phenomenon results from prolonged lung emptying due to bronchiolar narrowing or collapse(357). In BE, air trapping has been reported more frequently in association with bronchomalacia (358). It is a CT finding common to several respiratory conditions, including ILDs, asthma, and COPD (359); in COPD specifically, more severe air trapping has been associated with both the presence and extent of BE (360).

In CF, air trapping is particularly relevant, not only as a frequent finding, but more importantly, as a marker of early disease and a risk factor for disease progression (361–363). However, data on the significance of air trapping in BE are still limited. In patients with primary antibody deficiencies, such as CVID, specific antibody deficiency, or IgG subclass deficiency, it has been described as one of the most frequent CT abnormalities (364) (Grenier). In a study analysing patients with air trapping on CT, 38% also had BE, and notably, 30% had NTM infections. This unexpected overlap could indicate a selection bias (i.e., a population with higher NTM prevalence than typically reported among BE patients), or potentially a true correlation between the presence of atypical mycobacteria and air trapping (359).

In our study cohort, patients with and without air trapping only differed in FEV1 levels, that were lower in the first group.

On the other hand, radiological signs of air trapping were observed in a greater number of patients compared to those showing functional evidence of air trapping, with no correlation found between the two findings. This discrepancy may suggest that radiological alterations precede the development of irreversible functional impairment. However, given the limited sample size of the cohort, these findings should be interpreted with caution.

Considering CT findings together with lung function in our cohort, two different profiles seem to emerge. On one side, BWT and air trapping were associated with impaired lung function, characterized by lower post-BD FEV1 values and an obstructive pattern. On the other side, the presence of MP and GGO showed a strong correlation with BE extension, as reflected by Reiff index scores, the presence of cystic BE, and the number of affected lobes. This suggests that BWT and air trapping may be linked to dynamic changes involving the airways and possibly indicative of disease activity, and less influenced by bronchial remodelling. In contrast, MP and GGO might reflect long-term disease evolution, resulting in irreversible structural damage rather than functional impairment. This has potential clinical implications,

as it could enhance the role of radiological assessment beyond merely reporting BE stability or progression.

Apart from evaluating CT findings in their overall cohort, Pieters and colleagues also investigated the correlation between radiological patterns and specific aetiologies and comorbidities. In PCD, they observed a high prevalence of MP and inflammatory features such as GGO and BWT(339). These findings are consistent with previous studies on PCD, which have described a clear predominance of lower and middle lobe involvement, along with radiological signs of inflammation(356). In contrast, ABPA-related and post-infective BE demonstrated fewer inflammatory signs, suggesting a more stable disease phenotype with lower inflammatory activity (339). In patients with BE associated to asthma and COPD, the extent of BE was reduced, suggesting that their symptoms may be more attributable to greater involvement of the small airways rather than the larger airways, where BE are typically observed (339). IDP patients demonstrated reduced radiological severity, particularly with a lower extent of BE(339). This aligns with the fact that BE in immunocompromised patients typically develops as a consequence of infections, and its progression can be mitigated or prevented once the immune deficiency is diagnosed and treated, controlling the frequency of infections(365).

In our cohort, due to the limited sample size and the heterogeneity of aetiologies of our cohort, we were unable to assess the correlation between the underlying causes and comorbidities of BE and the observed radiological alterations.

In summary, radiological alterations in BE patients appear to be more varied, frequent, and clinically meaningful than bronchial dilatation alone. A comprehensive assessment of additional CT findings, such as emphysema, BWT, MP, GGO, and air trapping, may support etiological investigation, help identify patients with higher disease activity or risk of progression, and aid in the recognition of complications such as NTM or PA infections. Given that a full evaluation of BE CT scans is highly time-consuming and impractical in routine clinical settings, automated techniques are likely to play a key role in the future. These tools will not only assist researchers in deepening our understanding of the radiological manifestations of underlying biological processes, but also help translate this knowledge into more informed clinical decision-making.

6.9 DIAGNOSIS OF ASSOCIATED ASTHMA

To explore the coexistence of asthma in our bronchiectasis cohort, we applied a structured diagnostic approach incorporating clinical, functional, and biological criteria. While nearly

half of the patients (46.8%) met major clinical criteria for asthma, defined by the presence of at least two typical symptoms including wheezing or chest tightness with temporal variability, many lacked objective confirmation. Only a small number fulfilled functional criteria, and methacholine testing, though available in a limited subset, resulted negative in all subjects. Biological markers indicative of Th2-driven inflammation (elevated FeNO or blood eosinophilia) were present in 29 patients. However, in most of these cases, only one of the two markers was present, rather than both occurring in the same patient. Lastly, asthma was confirmed in only 4 patients (5%), with an additional 26.0% classified as "suspected asthma" based on suggestive clinical features without functional confirmation. In contrast, in 68.8% of the cohort, available data allowed for the exclusion of an asthma diagnosis.

The evaluation of asthma symptoms, as already stated, is not common nor standardized in BE patients. However, in our study more than half of the cohort referred a combination of symptoms suggestive of asthma, despite not fulfilling other suspicion criteria. An even larger proportion of patients presented isolated reports of wheezing or chest tightness, especially during infection. In this last case, we arbitrarily decided to not consider the clinical criteria fulfilled, to minimize the risk of asthma overdiagnosis in those individuals whose symptoms might be solely attributed to BE or to transient airway hyperreactivity during exacerbations.

However, the high prevalence of asthma-like symptoms in our cohort is of great clinical interest, considering its clinical implications. According to a survey on diagnostic delay in BE, one out of four BE patients referred having received an incorrect diagnosis and consequent treatment before the BE confirmation, almost half (49%) being mislabelled as asthmatics(366). It is possible that in BE patients wheezing and chest tightness represent the symptomatic expression of mechanisms different than bronchospasm. For example, the presence of chronic bronchial inflammation testified by the elevated prevalence of obstructive pattern and BWT in our cohort could lead to audible bronchospasm, especially during exacerbations or in presence of bronchomalacia. Also, similarly to what has already been proposed to explain postBD change, the presence of secretions and MP could condition transitory narrowing of the airway mimicking bronchoconstriction, that resolves after mobilization or expulsion of mucus.

Understanding the differences between the same symptom in different respiratory conditions could have an impact in patients' clinical outcomes, as the treatment of a symptom could not be effective if its cause is not addressed. This could represent a limitation to the "treatable traits" approach in patients were more than one disease is suspected or confirmed.

Similarly, the presence of confounding mechanisms in patients with BE and suspected asthma could require a revision of reference values in diagnostic tests, such as PBD test, FeNO or eosinophilia, through extensive population studies. Since no data about these differences has been published, we maintained the same functional and biological criteria considered diagnostic for asthma as in the normal population.

In order to increase insight of the functional profile of our patients, we additionally analysed and reported FEV1 variability over time, based on three spirometries performed in a stable state within a two-year period, to assess intrinsic fluctuations in lung function despite a normal bronchodilator response. However, we recognize that this approach is not a classical diagnostic criterion for asthma and may be influenced by various biases, including technical variability in lung function test execution (minimized by having the same team perform all tests using a standardized protocol and identical equipment), fluctuations in the patient's clinical status despite reported stability, and treatment modifications between different time points.

The most controversial criteria we included in our diagnostic criteria is the biological one: most biological findings described in asthmatic patients allow to assess the presence of a predominant T2 phenotype. Contrarily, no systemic markers of non-T2 asthma have been identified for clinical use. For technical reasons, we could not realize sputum cellularity in our patients; however, data suggest that levels of peripheral eosinophilia are suggestive of sputum eosinophil levels. On the other hand, sputum neutrophilia cannot be predicted on the bases of blood levels. Therefore, biological criteria included in the study can help identify only one specific endotype, without information on inflammation non T2 driven.

The use of FeNO has been previously proposed for the diagnosis of asthma in BE patients, Chen and colleagues evaluated FeNO levels in a BE cohort as a method to distinguish patients with and without concomitant asthma, confirmed by methacholine or PBD test (238). They found that a cut-off value of >22.5 ppb FeNO effectively differentiated asthmatic from non-asthmatic patients, with a sensitivity of 90.0% and specificity of 62.5%.

In our cohort, FeNO levels did not show significative differences between suspected/confirmed asthma patients and those where the comorbidity had been ruled out. However, patients without asthma showed significantly lower prevalences of values above the 25% cut-off (p=0.043). Considering FeNO levels >25 ppb in patients with confirmed or suspected asthma versus those in whom the diagnosis was excluded, we calculated a negative predictive value (NPV) of 77% (true negatives: patients without asthma and FeNO ≤25 ppb; false negatives: patients with asthma and FeNO ≤25 ppb). Based on this result,

FeNO may provide some guidance in ruling out asthma in bronchiectasis patients, but its moderate performance limits its use as a standalone exclusion test, while our data do not support its use in asthma diagnosis. However, these findings should be interpreted with caution, as the lack of methacholine testing limits the accurate identification of true asthmatic patients, especially those with T2 inflammation, potentially underestimating the role of FeNO.

Applying the pre-established study criteria for the diagnosis of asthma, the prevalence of this comorbidity in our cohort is surprisingly low, as only 3 patients fulfilled all criteria and one more patient was included in this group following investigators decision. In fact, despite the absence of biological criteria, as all the remaining criteria, questionnaire responses and history suggested a possible non-Th2 asthma phenotype. On the other hand, 26% of patients fulfilled clinical and inflammatory criteria, but could not be confirmed as asthmatic due to functional data: negative PBD and absence of methacholine. Altogether, patients with comorbid asthma diagnosed and suspected represent 31% off the cohort, the same prevalence of asthma observed in EMBARC registry, but only 5% could be fully confirmed.

The impossibility to perform methacholine represents a major limitation in the diagnosis of asthma in our study; in fact, it would have been necessary in at least 12 (15.6%) patients meeting all clinical and inflammatory criteria, showing a predominant Th2 inflammatory pattern, but lacking of a functional confirmation. In these patients, methacholine could help distinguish between a comorbid Th2 asthma or an eosinophilic BE phenotype.

While widely used in the general population for asthma diagnosis, methacoline is not routinely included in the assessment or follow-up of patients with BE, and only a few studies have investigated its utility in this specific subgroup.

A study in children with suspected asthma suggested that elevated IgE levels (>120 IU/mL), FeNO >23 ppb, and peripheral blood eosinophils >500 cells/μL could be predictive of methacholine positivity (367). In our cohort, only 1 patient in the suspected asthma subgroup fulfilled these criteria. On the other hand, in the general population poorer lung function parameters (particularly reduced FEV1, FEV1/FVC, and FEF25–75) are associated with increased methacholine responsiveness (368–370). However, these associations cannot be confidently extrapolated to BE patients due to the complex interplay of structural lung damage, chronic infection, and inflammation inherent to their primary disease. These factors profoundly influence both functional and inflammatory profiles, raising concerns about the reliability of conventional predictors of methacholine responsiveness in this population. Moreover, evidence from Shteinberg et al. indicates that

patients with eosinophilic BE, despite sharing some inflammatory features with those having BE and comorbid asthma related to T-driven inflammation, exhibit important differences, including a negative methacholine response in approximately 85% of cases tested(201).

Therefore, in the absence of methacholine challenge testing, we cannot definitively rule out asthma in patients from our suspected asthma subgroup. Nonetheless, taking into account previous studies reporting methacholine positivity rates in BE patients between 17% and 69% (138,371,372), it is unlikely that all patients classified in the suspected asthma group would have tested positive.

Interestingly, this also suggests that the prevalence of asthma reported in the EMBARC registry may be substantially overestimated. The frequent presence of clinical symptoms compatible with asthma in BE patients could have led many clinicians to attribute this comorbidity based solely on clinical judgment, without appropriate objective confirmation. While PBD testing can be feasibly incorporated into the diagnostic workup of all BE patients to assess for reversible airflow obstruction, methacholine challenge testing is more resource- and time-consuming, and should be reserved for selected cases.

Establishing clear clinical and/or biomarker-based criteria to identify which patients should undergo methacholine challenge testing would greatly assist in developing tailored, evidence-based diagnostic protocols for BE patients presenting with asthma-like symptoms.

As previously stated, we chose to group together and compare patients with a confirmed diagnosis of asthma and those in whom asthma was only suspected.

While this approach may seem to contrast with the study's objective of providing a precise and rigorous diagnosis of asthma in patients with BE, we believe it still offers relevant clinical insight. Specifically, it helps characterize a group of patients who, in everyday practice, would likely be labelled as asthmatic based solely on symptoms and biological features, without undergoing further diagnostic evaluation. Moreover, characteristics of the four patients with confirmed asthma were aligned with the "suspected asthma" group.

Unlike patients with BE and asthma described in previous studies, including analyses from the EMBARC registry, those in our cohort did not show significant differences in age and disease severity compared to BE patients without asthma. Similarly, the prevalence of CRS was comparable between the groups. However, they had a higher BMI and a longer duration of bronchiectasis since diagnosis.

Similarly to what was reported by EMBARC data, the two groups in our cohort showed comparable FEV_1 values (122). However, possibly asthmatic patients in our cohort had

significantly lower FVC and TLC, an unexpected finding that is difficult to explain based on the available data.

Our results also align with European data regarding the use of ICS, which was significantly more frequent among patients with suspected/confirmed asthma (75%) compared to those in whom asthma had been excluded (45%), despite the absence of differences in lung function(122). Given that none of the patients had a prior diagnosis of asthma at study entry, this finding suggests that ICS use may be driven by factors other than pulmonary function, such as the presence of wheezing or elevated blood eosinophils. In contrast to previous European data, no significant differences were observed between groups in terms of the use of long-term macrolides, inhaled antibiotics, or airway clearance techniques(122).

Regarding exacerbations, patients in our cohort showed similar frequencies of acute events across all groups. This contrasts with EMBARC data, where a diagnosis of asthma was associated with an increased risk of exacerbations and hospitalizations, but also with lower mortality, even after adjusting for clinical, demographic, and treatment-related variables. It is important to note that the EMBARC database is designed to register only infectious exacerbations; therefore, it provides no information on asthmatic exacerbations treated exclusively with oral corticosteroids (OCS). Similarly, in our study, we recorded only exacerbations treated with antibiotics, excluding those managed solely with OCS as well as viral exacerbations.

Also, radiological findings in our cohort were comparable between patients with and without suspected/confirmed asthma. However, those with a higher likelihood of comorbid asthma showed slightly greater BE severity, as assessed by the Reiff index. Mild scores were reported in 55% of this group, compared to 65% among non-asthmatic patients. Similarly, air trapping was more frequently observed in the suspected or confirmed asthma group (83%) than in non-asthmatics (64%). Although these differences were small and neither statistically nor clinically significant, it is noteworthy that expiratory scans were unavailable in 26.4% of the non-asthma group, compared to only 8% in the asthma-suspected or confirmed group. This may suggest a tendency to perform expiratory scans more frequently when air trapping is expected. Whether this practice reflects a decision made by respiratory physicians based on clinical signs and symptoms, or an initiative by radiologists based on inspiratory scan findings, cannot be determined.

Our findings suggest that radiological features alone are not sufficient to distinguish patients with comorbid asthma from those without, although some differences may raise clinical suspicion and warrant further investigation. To our knowledge, this is the first study to

attempt a comprehensive description of the radiological characteristics of patients with both BE and asthma. While reviewing literature, we found no published data specifically describing radiological features of asthmatic patients within a BE cohort. In contrast, existing studies have primarily focused on the presence of BE in asthma populations, without addressing broader radiological findings.

Despite providing a first radiological characterization of this subgroup, our study is limited by the small sample size, the use of manual and operator-dependent methods, and the retrospective nature of the imaging data. Larger studies, supported by digital technologies, are needed to enhance diagnostic accuracy and to better define the radiological profile of patients with coexisting BE and asthma.

Microbiology was similar between the two groups of our cohort in terms of CBI due to PA and other PPM, in line with data published from the EMBARC cohort. In the European registry some differences were shown in microbiology in relation to the presence of asthma, that showed higher rates of *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae*. Differences in microbiology did not show any correlation with the increased rate of exacerbations. We could not verify these data in our cohort, as isolates other than *PA* were not enough to be properly analysed.

Notably, no differences were observed in QoL questionnaires between the groups, including ACT scores. This may be related to the enrolment criteria, which excluded patients with a known asthma diagnosis. Individuals with more severe or uncontrolled asthma symptoms are more likely to receive a diagnosis, whereas those with milder clinical presentations may remain undiagnosed. As a result, our cohort likely included only patients with mild, well-controlled symptoms, in whom asthma suspicion was low or absent prior to the study. In conclusion, the diagnosis of asthma in our cohort was not associated with major differences in instrumental assessments, with only a few exceptions. Patients with confirmed or suspected asthma showed higher BMI, longer time since BE diagnosis, comparable FEV1 values but greater use of ICS, and a tendency toward increased BE radiological extension and more frequent air trapping. However, unlike findings reported in other cohorts, no differences were observed in disease severity, exacerbation rate, or quality of life.

6.10 DIAGNOSIS OF ASSOCIATED COPD

In our study, less than 10% of patients met ROSE criteria, having an obstructive pattern and a documented exposure. These patients showed a trend to lower FEV1 percentages of predicted values compared to non-COPD subjects, with median values of 67.5% and 81%,

respectively. They also had less extensive BE, with 83% classified as having mild disease according to the Reiff score, compared to 61% of patients with BE without COPD.

As discussed earlier, the exclusion of patients with a documented COPD diagnosis might be the main factor contributing to the discrepancy between our data and literature. At our centre, we adopted the ROSE criteria immediately after its publication, motivated by our specific interest in the topic due to active participation in the study, as well as the ease of use of these criteria. As a result, most patients with COPD in follow up in our centre had already received a diagnosis prior to inclusion. This has led to a smaller COPD population in our study and has limited our ability to draw definitive conclusions and make robust comparisons with other published studies. Nonetheless, we chose to maintain a consistent approach to asthma and COPD diagnosis. Including patients with pre-existing diagnoses could have introduced several biases. For example, patient selection might have unintentionally favoured one diagnosis over another, leading to skewed data. Additionally, the impact of comorbidities on disease severity may have led to less interpretable findings, due to the difficulty in distinguishing the contribution of each condition and may have resulted in a sample that is not fully representative of the broader BE population.

However, these limitations could have impacted in our observed results. In fact, in comparison to previous literature, the prevalence of BE-COPD patients in our study is notably lower. The lack of statistical significance for most comparisons is likely influenced by this marked imbalance in group sizes, with only 7 patients in the COPD group versus 70 in the non-COPD group, which substantially limits statistical power and the ability to detect meaningful differences. We did not find any other statistically significant difference in terms of demographic characteristics, disease severity, treatment, microbiology, exacerbation rates, QoL (including CAT) and inflammatory markers (blood eosinophils, FeNO levels, IgE).

However, some findings deserve closer examination, as certain differences, though not statistically significant, may still hold clinical relevance. This is the case for FEV1 percentage of predicted: both mean and median FEV1 values in the non-COPD population remained within the normal range, whereas patients with BE and COPD showed, on average, a moderate reduction in FEV1. Specifically, the mean FEV1% was 81.83 (SD 20.33) in pure BE compared with 72.17% (SD 19.28) in the BE-COPD group. Moreover, despite the lack of significance, we could notice that *PA* infection was slightly more prevalent among patients with COPD, being observed in 66% of subjects in this subgroup compared with 40% of the non-COPD population, in line with previously reported data (121).

Patients with COPD in our cohort did not exhibit greater disease severity compared to non-COPD patients, in contrast with previously published cohorts. However, it is noteworthy that a smaller proportion of individuals in the BE+COPD group were classified as having mild disease according to the BSI (14% vs 42%). This numerical difference was not reflected in the FACED score. This discrepancy may be explained by the different weighting of variables in the two indices. Additionally, scores close to the threshold between mild and moderate categories could have impacted in this divergence.

In summary, patients with comorbid COPD showed overall similar characteristics compared to those with bronchiectasis alone, despite a lower radiological extent of disease and a tendency toward reduced FEV1 values. However, the small sample size likely limited the statistical power of our analysis and may account for the lack of significant differences.

6.11 DIAGNOSIS OF ASSOCIATED CRS

CRS was diagnosed in 23 of 73 patients (31.5%), mostly based on clinical evaluation, with only a minority confirmed by imaging or endoscopy. CRS with nasal polyps was found in 4 patients. SNOT-22 scores were significantly higher in CRS patients, particularly for nasal, ear, facial pain, and fatigue symptoms, reflecting a greater upper airway burden. While most variables did not show any relevant difference between patients with and without CRS, those diagnosed with the disease presented higher volumes of sputum and slightly lower radiological extent.

The prevalence of CRS in our cohort falls within the broad range reported in the literature (7–75%) and is higher than the 21% reported in the European registry (89,101,200,202–206,209). This discrepancy may partly reflect methodological differences: the EMBARC registry collected only clinician-reported CRS diagnoses without specific tools to assess UAS. This highlights the risk of underestimation of real CRS prevalence, as UAS are often overlooked in pulmonology evaluations, despite their relevance. In COPD, for example, a study showed that 82% of patients ultimately diagnosed with CRS had never previously been assessed for upper airway involvement (69). While similar data are lacking for BE, similar underdiagnosis is plausible. In our cohort, four patients with a history of nasal polyp surgery were included in the study as their prior surgeries were not documented in BE follow-up records, highlighting a broader trend of poor UAS documentation, even in a specialized tertiary care setting. This underreporting highlights the need for systematic UAS evaluation in BE.

Among patients with symptoms consistent with EPOS criteria, those who underwent further assessment all had CRS confirmed by imaging and/or endoscopy. Furthermore, SNOT-22 scores were significantly higher in patients with CRS. Our results align with a study by Guillemany and colleagues, that evaluated SNOT-22 results in BE patients, finding significantly higher scores in BE patients with CRS compared to those without CRS. Moreover, they observed that mean SNOT-22 score in their cohort exceeded that of the general population used for the original validation of the questionnaire, suggesting higher burden of UAS in BE even in absence of CRS (373). On the other hand, in our cohort we observed significantly higher scores for all domains typical of CRS (nose and ear related, night symptoms, facial pain), while elements commonly shared with BE such as cough, psycho-social impact did not differ between groups. This suggests that patients with confirmed CRS present a distinct symptomatologic profile, not derived by the presence of BE.

The consistency between clinical symptoms, instrumental confirmation, and SNOT-22 domains in our cohort supports the applicability of EPOS criteria for diagnosing CRS in BE patients, despite the unique features of this population.

Conversely, our data did not confirm a clear association between CRS and asthma in BE. Although the number of patients with confirmed asthma was small, no differences emerged even when including patients with suspected asthma. The presence or absence of CRS did not meaningfully predict nor rule out asthma diagnosis. These findings support the existence of a CRS-BE phenotype that is independent from asthma.

In our study, the CRS-BE phenotype showed a lower extent of bronchiectasis, with fewer lobes involved and lower Reiff scores. This data seems to be in contradiction with the literature, as previous studies showed more radiological extension and risk of BE progression in patients with CRS(206,216). Despite this milder radiological presentation, these patients exhibited higher sputum volumes, while exacerbation rates and lung function values were comparable to those observed in the overall BE population. This apparent discrepancy suggests that the upper airway inflammation typical of CRS may contribute to symptoms, particularly sputum production, and acute episodes, independently of the extent of structural bronchial damage. This hypothesis, together with the burden and impact on quality of life of UAS observed with SNOT22, highlights the need for increased attention to these symptoms not only to identify patients with CRS and avoid underestimation of a possibly milder radiological but not clinical disease, but also to guarantee correct management of UAS in all BE patients.

The EPOS symptom questionnaire could serve as a practical tool to screen for compatible symptoms and guide the need for further upper airway evaluation or ENT referral. Given its simplicity and speed, it could be easily integrated into the routine assessment performed during the etiological workup of BE.

6.11 PATIENTS WITH PURE BE VS COMORBIDITIES

The percentage of patients with at least one comorbidity, confirmed or highly suspected, in our cohort reached almost the 60% of patients. However, the comparison between patients with pure BE and those with other AWDs did not evidence any significant difference.

These findings are particularly interesting and carry several important implications. First, the unexpectedly high prevalence of comorbidities is striking—especially considering that these conditions had not been previously diagnosed before enrolment in the study. This underscores the need to actively consider the possibility of a second airway disease, even when bronchiectasis alone appears sufficient to account for the clinical presentation.

It also points to the value of broadening the standard diagnostic approach. Incorporating a more comprehensive set of clinical and instrumental assessments—such as specific questionnaires, complete lung function testing, and systematic evaluation of radiological features beyond bronchiectasis—can help identify coexisting airway diseases or relevant “treatable traits.” This extended assessment should be considered at least at the time of initial evaluation.

The observation that patients with “pure” bronchiectasis exhibit similar characteristics to those with comorbidities may be explained by the overlapping and potentially counterbalancing effects of each comorbid condition. These interactions may obscure specific patterns when comorbidities are assessed collectively, contributing to their underdiagnosis. This further supports the importance of evaluating each comorbidity independently.

Larger studies are needed to validate these findings and guide the development of systematic strategies for the detection and management of comorbidities in bronchiectasis patients.

7. CONCLUSIONS

1. In patients with BE, symptoms not traditionally considered typical of the disease, such as wheezing and upper airway symptoms, are frequently reported, even in the absence of other airway comorbidities (i.e. asthma or CRS). While the presence of these symptoms should prompt clinicians to investigate possible coexisting respiratory conditions, they are not, on their own, sufficient to establish a diagnosis.

2. The spectrum of radiological and functional alterations in patients with bronchiectasis is broad and heterogeneous, extending beyond the parameters most commonly assessed, such as FEV1 and the extent of bronchiectasis. While the interplay between these variables remains poorly understood, it may hold potential for refining diagnostic and prognostic approaches for BE patients, particularly in the evaluation of coexisting airway diseases. This variability highlights the need for a more comprehensive instrumental assessment in this population.

3. Although these questionnaires do not seem to contribute in defining BE phenotypes related to the existence of associated AWDs, they reinforce the value of patient-reported outcomes to establish therapeutic goals in BE. The systematic use of generic and disease- or symptom-specific quality of life questionnaires may enhance the multidimensional assessment of BE patients and help in guiding the therapeutic strategy aimed not only at improving clinical outcomes but also at enhancing patients' overall quality of life.

4. Airway comorbidities are common in bronchiectasis and may often go undiagnosed in clinical practice. Although the specific features of each comorbidity combination are difficult to clearly define, the coexistence of another airway disease can influence clinical presentation and outcomes in distinct ways, depending on the nature of the comorbidity involved.

5. Despite the fact that diagnosis of associated asthma has been reported in up to 30% of BE patients, a complete investigation of this condition, through clinical, biological and functional criteria, shows that its prevalence is much lower. This overestimation of asthma prevalence in BE could be the result of the misleading frequent report of wheezing in BE, but also the consequence of the fact we lack of a standard definition of the association of asthma and BE and of a specific diagnostic protocol to assess it.

6. A complete investigation also resulted in a diagnosis of CRS in about a third of all BE patients. These individuals presented more sputum expectoration, the symptom that usually contributes most to deteriorate QoL in BE, although no worse clinical outcomes were detected. The detection of CRS through a standardized protocol could be

essential to improve patients' QoL but also to personalized the therapy as the presence of CRS has been reported in association with predominant Th2 inflammatory profile, and this could lead to specific therapeutic approach.

8. FUTURE DIRECTIONS

In our study, we aimed at assessing the presence and the characteristics of the most frequent AWD in a cohort of BE patients. To achieve this, we attempted to phenotype our BE patients by evaluating a broad range of clinical, instrumental, and biological variables that are not typically included in routine BE assessments.

As a result, several lines of research may follow this study, focusing either on expanding the traditional clinical management of the disease or on improving the diagnosis and treatment of airway comorbidities.

Atypical symptoms in BE: among the most interesting findings of this study is the high frequency of symptoms that are not considered as hallmarks of BE, such as wheezing and UAS, whose prevalence is poorly described or completely ignored when describing BE clinical presentation in literature. In particular, the pathophysiology behind the development of wheezing in BE could be different from asthma and its identification could inform, therefore, of other abnormalities such as mucus plugging or bronchial wall thickening. Their management might therefore represent an unmet need in this population and the role of these symptoms should be better investigated in order to avoid, for instance, over-diagnosis of asthma or underestimation of CRS. The inclusion of these “atypical” signs and symptoms in future studies with greater numerosity could help identify their true prevalence in the BE population and assess their impact on QoL. Moreover, these symptoms could represent treatable traits for new anti-inflammatory drugs, and their management could be included among the outcomes assessed in future drug development.

- **Role of Instrumental Tests in the Management of BE: Beyond FEV1.** While spirometry remains the most commonly used instrumental test for the follow-up of BE, its clinical relevance in this context is limited. Conversely, little is known about the role of other lung function tests and respiratory assessments, such as body plethysmography, DLCO, PBD testing, and FeNO measurement, in the evaluation of BE patients.

  In our study, we identified functional abnormalities largely beyond the pure definition of airway obstruction and the reduction in FEV1, consistent with findings from previous studies. However, the clinical significance and prognostic implications of these alterations remain unclear. Future, larger studies are needed to define which combination of tests can provide the most comprehensive and accurate phenotypic characterization of BE patients. Such efforts could help meet the need for outcome measures that support risk stratification, the identification of respiratory

comorbidities, and the identification of treatable traits to improve personalization of management.

- **Role of radiology in the AI era.** Despite being primarily a radiological diagnosis, in BE the use of radiology has been mainly directed toward the assessment of bronchial dilatation severity and to assess the presence of complications. However, in our study we identified an unexpected proportion of other radiological features, whose significance and prognostic values are limited by the small size of the cohort. Moreover, the use of analogical quantification prevented the accurate qualitative and quantitative description of these radiological findings, reducing their interpretability. The use of AI could solve both these problems, as already existing AI-based software for CT interpretation could help define radiological phenotypes, their correlation with clinical phenotypes and airways comorbidities, and the possible role in management and chronic treatment outcomes by the automated analysis of huge number of images.

- **Standardization of airways comorbidity diagnosis.** The diagnosis of airways comorbidities in BE represents an ongoing challenge, both in terms of diagnostic procedures and clinical impact. Objective criteria have been proposed only for COPD, with the introduction of the ROSE criteria. The diagnosis of CRS appears more straightforward, and our data suggest that the application of CRS diagnostic criteria in BE patients is feasible and could be clinically relevant. On the other hand, the diagnosis of asthma is considerably more complex due to the heterogeneity of its clinical presentations, the flexibility of diagnostic criteria even in the general population, and the need for instrumental confirmation, which may not be available in certain settings. This results in wide variability in reported prevalence across studies and a high risk of misdiagnosis. Our data suggest that relying on clinical presentation alone may be misleading in a significant proportion of cases.

  Future studies involving larger cohorts are needed to help identify objective criteria and develop diagnostic algorithms, which should then be validated in international cohorts and implemented in clinical practice. In the coming months, we are planning an extension of the study in which we will perform methacholine challenge testing in all subjects with suspected asthma, as well as in a proportion of those in whom asthma has been previously excluded, to evaluate its role in confirming the diagnosis and to help determine the true prevalence of asthma in our cohort.

- **Development of clinical tools for diagnosis of AW comorbidities in BE.** Our study suggests the presence of clinical differences between patients with and without other AWDs, although this finding is greatly limited by the small sample size. Studies on larger cohorts may allow for the identification of clinical characteristics suggestive of AWDs in BE patients, ultimately leading to the development of fast, feasible, and easy-to-use screening tools. These tools could be implemented in clinical practice to identify patients who should undergo instrumental confirmation of concomitant AWDs.

9. BIBLIOGRAPHY

1. Momtazmanesh S, Moghaddam SS, Ghamari S-H, Rad EM, Rezaei N, Shobeiri P, et al. Global burden of chronic respiratory diseases and risk factors, 1990–2019: an update from the Global Burden of Disease Study 2019. eClinicalMedicine [Internet]. 2023 May;59:101936. Available from: https://linkinghub.elsevier.com/retrieve/pii/S258953702300113X

2. Pettigrew HD, Chang C, Teuber SS, Gershwin ME. The Clinical Definitions of Asthma. In: Bronchial Asthma. Springer New York; 2012. p. 3–18.

3. Shampo MA, Kyle RA. Nei Ching—Oldest Known Medical Book. Mayo Clin Proc [Internet]. 1989 Jan 1;64(1):134. Available from: https://doi.org/10.1016/S0025-6196(12)65320-8

4. Cohen SG. Asthma in Antiquity: The Ebers Papyrus. Allergy Asthma Proc [Internet]. 1992 May 1;13(3):147–54. Available from: http://www.ingentaconnect.com/content/10.2500/108854192778878746

5. Laennec RTH, Ramadge FH, Laennec M, A GA. A Treatise on Diseases of the Chest. Medico-chirurgical Rev J Med Sci Anal Ser [Internet]. 1822 Mar 1;2(8):795–808. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29917441

6. Petty TL. The history of COPD. Int J COPD [Internet]. 2006 Jan;1(1):3–14. Available from: http://www.atypon-link.com/DMP/doi/abs/10.2147/copd.2006.1.1.3

7. Briscoe WA, Nash ES. THE SLOW SPACE IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE*. Ann N Y Acad Sci [Internet]. 1965 Mar 16;121(3):706–22. Available from: https://nyaspubs.onlinelibrary.wiley.com/doi/10.1111/j.1749-6632.1965.tb14239.x

8. Fletcher C, Peto R, Tinker C SF. The natural history of chronic bronchitis and emphysema. An eight-year study of early chronic obstructive lung disease in working men in London. London; 1978.

9. Laennec, R. T. H. (René Théophile Hyacinthe) 1781-1826.;, Forbes, John, Sir, 1787-1861 T., Fisher, John D. (John Dix), 1797-1850 T., Andral, G. (Gabriel) 1797-1876. A Treatise on the Diseases of the Chest, and on Mediate Auscultation. Medico-chirurgical Rev [Internet]. 1829 Apr 1;10(20):420–2. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29919206

10. Wrong O. Osler and my father. JRSM [Internet]. 2003 Sep 1;96(9):462–4. Available from: http://jrsm.rsmjournals.com/cgi/doi/10.1258/jrsm.96.9.462

11. Geddes D. The history of respiratory disease management. Medicine (Baltimore) [Internet]. 2020 Apr;48(4):239–43. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1357303920300219

12. Kouri A, Dandurand RJ, Usmani OS, Chow C-W. Exploring the 175-year history of spirometry and the vital lessons it can teach us today. Eur Respir Rev [Internet]. 2021 Dec 31;30(162):210081. Available from: http://publications.ersnet.org/lookup/doi/10.1183/16000617.0081-2021

13. Hatabu H, Madore B. Dark-Field Chest X-ray Imaging: An Evolving Technique in the Century-Old History of Chest X-ray Imaging. Radiology [Internet]. 2021 Nov;301(2):396–7. Available from: http://pubs.rsna.org/doi/10.1148/radiol.2021211603

14. Venkatesan P. 2023 GINA report for asthma. Lancet Respir Med [Internet]. 2023 Jul;11(7):589. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2213260023002308

15. Miller RL, Grayson MH, Strothman K. Advances in asthma: New understandings of asthma's natural history, risk factors, underlying mechanisms, and clinical management. J Allergy Clin Immunol [Internet]. 2021 Dec;148(6):1430–41. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0091674921015232

16. Cruz MJ, Romero-Mesones C, Muñoz X. ¿Puede la contaminación ambiental causar asma? Arch Bronconeumol [Internet]. 2018 Mar;54(3):121–2. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0300289617303046

17. Kuruvilla ME, Lee FE-H, Lee GB. Understanding Asthma Phenotypes, Endotypes, and Mechanisms of Disease. Clin Rev Allergy Immunol [Internet]. 2019 Apr 11;56(2):219–33. Available from: http://link.springer.com/10.1007/s12016-018-8712-1

18. Kaur R, Chupp G. Phenotypes and endotypes of adult asthma: Moving toward precision medicine. J Allergy Clin Immunol [Internet]. 2019 Jul;144(1):1–12. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0091674919307535

19. Borish L. The immunology of asthma. Ann Allergy, Asthma Immunol [Internet]. 2016 Aug;117(2):108–14. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1081120616301806

20. White SR, Martin LD, Stern R, Laxman B, Marroquin BA. Expression of IL-4/IL-13 receptors in differentiating human airway epithelial cells. Am J Physiol Cell Mol Physiol [Internet]. 2010 Nov;299(5):L681–93. Available from: https://www.physiology.org/doi/10.1152/ajplung.00422.2009

21. Raundhal M, Morse C, Khare A, Oriss TB, Milosevic J, Trudeau J, et al. High IFN-γ and low SLPI mark severe asthma in mice and humans. J Clin Invest [Internet]. 2015 Aug 3;125(8):3037–50. Available from: http://www.jci.org/articles/view/80911

22. Al-Ramli W, Préfontaine D, Chouiali F, Martin JG, Olivenstein R, Lemière C, et al. TH17-associated cytokines (IL-17A and IL-17F) in severe asthma. J Allergy Clin Immunol [Internet]. 2009 May;123(5):1185–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0091674909003479

23. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. Nat Med [Internet]. 2012 May 4;18(5):716–25. Available from: https://www.nature.com/articles/nm.2678

24. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster Analysis and Clinical Asthma Phenotypes. Am J Respir Crit Care Med [Internet]. 2008 Aug 1;178(3):218–24. Available from: https://www.atsjournals.org/doi/10.1164/rccm.200711-1754OC

25. Plaza Moral V, Alobid I, Álvarez Rodríguez C, Blanco Aparicio M, Ferreira J, García G, et al. GEMA 5.3. Spanish Guideline on the Management of Asthma. Open Respir Arch [Internet]. 2023 Oct;5(4):100277. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2659663623000632

26. Aliberti S, Goeminne PC, MD AEO, Aksamit TR, Al-Jahdali H, Barker AF, et al. Consensus definitions of bronchiectasis for use in clinical trials - a joint working group of EMBARC and the United States BRR. Manuscr under Rev. 2020;

27. Javidan-Nejad C, Bhalla S. Bronchiectasis. Radiol Clin North Am [Internet]. 2009 Mar;47(2):289–306. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0033838908002170

28. Flume PA, Chalmers JD, Olivier KN. Advances in bronchiectasis: endotyping, genetics, microbiome, and disease heterogeneity. Lancet [Internet]. 2018 Sep;392(10150):880–90. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673618317677

29. Cole PJ. Inflammation: a two-edged sword--the model of bronchiectasis. Eur J Respir Dis Suppl [Internet]. 1986;147:6–15. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3533593

30. Araújo D, Shteinberg M, Aliberti S, Goeminne PC, Hill AT, Fardon T, et al. Standardised classification of the aetiology of bronchiectasis using an objective algorithm. Eur Respir J [Internet]. 2017 Dec 14 [cited 2021 Mar 18];50(6):1701289. Available from: http://dx.doi.org/10.1183/13993003.01289-2017.

31. Shoemark A, Ozerovitch L, Wilson R. Aetiology in adult patients with bronchiectasis. Respir Med [Internet]. 2007 Jun [cited 2019 Jul 10];101(6):1163–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17223027

32. Martinez-García MA, Villa C, Dobarganes Y, Girón R, Maíz L, García-Clemente M, et al. RIBRON: el registro español informatizado de bronquiectasias. Caracterización de los primeros 1.912 pacientes. Arch Bronconeumol [Internet]. 2021 Jan;57(1):28–35. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0300289620300041

33. Bush A, Floto RA. Pathophysiology, causes and genetics of paediatric and adult bronchiectasis. Respirology [Internet]. 2019 Nov 1 [cited 2021 Nov 24];24(11):1053–62. Available from: https://pubmed.ncbi.nlm.nih.gov/30801930/

34. McShane PJ. Common Variable Immunodeficiency and Other Immunodeficiency Syndromes in Bronchiectasis. Semin Respir Crit Care Med [Internet]. 2021 Aug;42(4):525–36. Available from: http://www.ncbi.nlm.nih.gov/pubmed/34261177

35. Shoemark A, Dell S, Shapiro A, Lucas JS. ERS and ATS diagnostic guidelines for primary ciliary dyskinesia: similarities and differences in approach to diagnosis. Eur Respir J [Internet]. 2019 Sep;54(3). Available from: http://www.ncbi.nlm.nih.gov/pubmed/31488586

36. Shoemark A, Griffin H, Wheway G, Hogg C, Lucas JS, Camps C, et al. Genome sequencing reveals underdiagnosis of primary ciliary dyskinesia in bronchiectasis. Eur Respir J [Internet]. 2022 Nov;60(5):2200176. Available from: http://erj.ersjournals.com/lookup/doi/10.1183/13993003.00176-2022

37. Fırat M, Mutlu Ş, Yoleri B, Boşnak Güçlü M. Comparison of respiratory functions, muscle strength, and physical activity among children with primary ciliary dyskinesia with and without Kartagener's syndrome and healthy controls. Physiother Theory Pract [Internet]. 2023 Nov 28;1–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/38018157

38. Sreekumar V, Norris DP. Cilia and development. Curr Opin Genet Dev [Internet]. 2019 Jun;56:15–21. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0959437X18300984

39. Polineni D, Davis SD, Dell SD. Treatment recommendations in Primary Ciliary Dyskinesia. Paediatr Respir Rev [Internet]. 2016 Mar;18:39–45. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/26586601

40. Su Y, Zhang Y, Chai Y, Xu J. Autoimmune diseases and their genetic link to bronchiectasis: insights from a genetic correlation and Mendelian randomization study. Front Immunol [Internet]. 2024;15:1343480. Available from: http://www.ncbi.nlm.nih.gov/pubmed/38660310

41. Cavalli CAM, Gabbiadini R, Dal Buono A, Quadarella A, De Marco A, Repici A, et al. Lung Involvement in Inflammatory Bowel Diseases: Shared Pathways and Unwanted Connections. J Clin Med [Internet]. 2023 Oct 9;12(19). Available from: http://www.ncbi.nlm.nih.gov/pubmed/37835065

42. O'Donnell AE. Bronchiectasis — A Clinical Review. Taichman DB, editor. N Engl J Med [Internet]. 2022 Aug 11;387(6):533–45. Available from: http://www.nejm.org/doi/10.1056/NEJMra2202819

43. Polverino E, Goeminne PC, McDonnell MJ, Aliberti S, Marshall SE, Loebinger MR, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. Eur Respir J [Internet]. 2017;50(3). Available from: http://dx.doi.org/10.1183/13993003.00629-2017

44. Terry PD, Dhand R. The 2023 GOLD Report: Updated Guidelines for Inhaled Pharmacological Therapy in Patients with Stable COPD. Pulm Ther [Internet]. 2023 Sep 20;9(3):345–57. Available from: https://link.springer.com/10.1007/s41030-023-00233-z

45. Ministerio de Sanidad. Informe Anual del Sistema Nacional de Salud 2022 - Resumen ejecutivo. Dep Salud [Internet]. 2023;1–43. Available from: https://cpage.mpr.gob.es

46. Rabe KF, Watz H. Chronic obstructive pulmonary disease. Lancet [Internet]. 2017 May;389(10082):1931–40. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673617312229

47. Adeloye D, Song P, Zhu Y, Campbell H, Sheikh A, Rudan I. Global, regional, and national prevalence of, and risk factors for, chronic obstructive pulmonary disease (COPD) in 2019: a systematic review and modelling analysis. Lancet Respir Med [Internet]. 2022 May;10(5):447–58. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2213260021005117

48. Sin DD, Doiron D, Agusti A, Anzueto A, Barnes PJ, Celli BR, et al. Air pollution and COPD: GOLD 2023 committee report. Eur Respir J [Internet]. 2023 May;61(5):2202469. Available from: http://erj.ersjournals.com/lookup/doi/10.1183/13993003.02469-2022

49. Strange C. Alpha-1 Antitrypsin Deficiency Associated COPD. Clin Chest Med [Internet]. 2020 Sep;41(3):339–45. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0272523120300290

50. Silverman EK. Genetics of COPD. Annu Rev Physiol [Internet]. 2020 Feb 10;82(1):413–31. Available from: https://www.annualreviews.org/doi/10.1146/annurev-physiol-021317-121224

51. Kabesch M, Adcock IM. Epigenetics in asthma and COPD. Biochimie [Internet]. 2012 Nov;94(11):2231–41. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0300908412002994

52. Hogg JC, Timens W. The Pathology of Chronic Obstructive Pulmonary Disease. Annu Rev Pathol Mech Dis [Internet]. 2009 Feb 1;4(1):435–59. Available from: https://www.annualreviews.org/doi/10.1146/annurev.pathol.4.110807.092145

53. Fischer B, Voynow J, Ghio A. COPD: balancing oxidants and antioxidants. Int J Chron Obstruct

Pulmon Dis [Internet]. 2015 Feb;261. Available from: http://www.dovepress.com/copd-balancing-oxidants-and-antioxidants-peer-reviewed-article-COPD

54. Miravitlles M. Alpha-1-antitrypsin and other proteinase inhibitors. Curr Opin Pharmacol [Internet]. 2012 Jun;12(3):309–14. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1471489212000276

55. Villaseñor-Altamirano AB, Jain D, Jeong Y, Menon JA, Kamiya M, Haider H, et al. Activation of CD8 + T Cells in Chronic Obstructive Pulmonary Disease Lung. Am J Respir Crit Care Med [Internet]. 2023 Dec 1;208(11):1177–95. Available from: https://www.atsjournals.org/doi/10.1164/rccm.202305-0924OC

56. Ong J, Faiz A, Timens W, van den Berge M, Terpstra MM, Kok K, et al. Marked TGF-β-regulated miRNA expression changes in both COPD and control lung fibroblasts. Sci Rep [Internet]. 2019 Dec 3;9(1):18214. Available from: https://www.nature.com/articles/s41598-019-54728-4

57. van Geffen W, Kerstjens H. Static and dynamic hyperinflation during severe acute exacerbations of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis [Internet]. 2018 Apr;Volume 13:1269–77. Available from: https://www.dovepress.com/static-and-dynamic-hyperinflation-during-severe-acute-exacerbations-of-peer-reviewed-article-COPD

58. Yaghi A, Dolovich M. Airway Epithelial Cell Cilia and Obstructive Lung Disease. Cells [Internet]. 2016 Nov 11;5(4):40. Available from: http://www.mdpi.com/2073-4409/5/4/40

59. Nussbaumer-Ochsner Y, Rabe KF. Systemic Manifestations of COPD. Chest [Internet]. 2011 Jan;139(1):165–73. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0012369211600299

60. Osadnik CR, Tee VS, Carson-Chahhoud K V, Picot J, Wedzicha JA, Smith BJ. Non-invasive ventilation for the management of acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease. Cochrane Database Syst Rev [Internet]. 2017 Jul 13;2017(7). Available from: http://doi.wiley.com/10.1002/14651858.CD004104.pub4

61. Dietz de Loos D, Lourijsen ES, Wildeman MAM, Freling NJM, Wolvers MDJ, Reitsma S, et al. Prevalence of chronic rhinosinusitis in the general population based on sinus radiology and symptomatology. J Allergy Clin Immunol. 2019 Mar;143:1207–14.

62. Hastan D, Fokkens WJ, Bachert C, Newson RB, Bislimovska J, Bockelbrink A, et al. Chronic rhinosinusitis in Europe - an underestimated disease. A GA2LEN study. Allergy. 2011 Sep;66(9):1216–23.

63. Palmer JN, Messina JC, Biletch R, Grosel K, Mahmoud RA. A cross-sectional, population-based survey of U.S. adults with symptoms of chronic rhinosinusitis. Allergy Asthma Proc [Internet]. 2019 Jan 14;40(1):48–56. Available from: https://www.ingentaconnect.com/content/10.2500/aap.2019.40.4182

64. Hirsch AG, Stewart WF, Sundaresan AS, Young AJ, Kennedy TL, Scott Greene J, et al. Nasal and sinus symptoms and chronic rhinosinusitis in a population-based sample. Allergy [Internet]. 2017 Feb;72(2):274–81. Available from: https://onlinelibrary.wiley.com/doi/10.1111/all.13042

65. DeConde AS, Soler ZM. Chronic Rhinosinusitis: Epidemiology and Burden of Disease. Am J Rhinol Allergy [Internet]. 2016 Mar 1;30(2):134–9. Available from:

https://journals.sagepub.com/doi/10.2500/ajra.2016.30.4297

66. Massoth L, Anderson C, McKinney KA. Asthma and Chronic Rhinosinusitis: Diagnosis and Medical Management. Med Sci [Internet]. 2019 Mar 27;7(4):53. Available from: https://www.mdpi.com/2076-3271/7/4/53

67. Andersson A, Bergqvist J, Lindberg A, Zhou C, Nyberg F, Hellgren J, et al. Chronic rhinosinusitis in COPD is associated with increased exacerbation risk. In: Monitoring airway disease [Internet]. European Respiratory Society; 2023. p. PA3624. Available from: http://publications.ersnet.org/lookup/doi/10.1183/13993003.congress-2023.PA3624

68. Øie MR, Dahlslett SB, Sue-Chu M, Helvik A-S, Steinsvåg SK, Thorstensen WM. Rhinosinusitis without nasal polyps in COPD. ERJ Open Res [Internet]. 2020 Apr 5;6(2):00015–2020. Available from: http://publications.ersnet.org/lookup/doi/10.1183/23120541.00015-2020

69. Arndal E, Sørensen AL, Lapperre TS, Said N, Trampedach C, Aanæs K, et al. Chronic rhinosinusitis in COPD: A prevalent but unrecognized comorbidity impacting health related quality of life. Respir Med [Internet]. 2020 Sep;171:106092. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0954611120302328

70. Brunner J, Riley C, McCoul E. A Systematic Review of the Treatment of Chronic Rhinosinusitis in Adults with Primary Ciliary Dyskinesia. Sinusitis [Internet]. 2017 Jan 26;2(1):1. Available from: https://www.mdpi.com/2673-351X/2/1/1

71. Lam YT, Papon J-F, Alexandru M, Anagiotos A, Armengot M, Boon M, et al. Sinonasal disease among patients with primary ciliary dyskinesia: an international study. ERJ Open Res [Internet]. 2023 May;9(3):00701–2022. Available from: http://publications.ersnet.org/lookup/doi/10.1183/23120541.00701-2022

72. Habib A-RR, Buxton JA, Singer J, Wilcox PG, Javer AR, Quon BS. Association between Chronic Rhinosinusitis and Health-Related Quality of Life in Adults with Cystic Fibrosis. Ann Am Thorac Soc [Internet]. 2015 May 26;150526140002000. Available from: http://www.atsjournals.org/doi/10.1513/AnnalsATS.201504-191OC

73. Habib AR, Quon BS, Buxton JA, Alsaleh S, Singer J, Manji J, et al. The Sino-Nasal Outcome Test–22 as a tool to identify chronic rhinosinusitis in adults with cystic fibrosis. Int Forum Allergy Rhinol [Internet]. 2015 Dec 30;5(12):1111–7. Available from: https://onlinelibrary.wiley.com/doi/10.1002/alr.21607

74. Krajewska J, Zub K, Słowikowski A, Zatoński T. Chronic rhinosinusitis in cystic fibrosis: a review of therapeutic options. Eur Arch Oto-Rhino-Laryngology [Internet]. 2022 Jan 22;279(1):1–24. Available from: https://link.springer.com/10.1007/s00405-021-06875-6

75. Orlandi RR, Kingdom TT, Smith TL, Bleier B, DeConde A, Luong AU, et al. International consensus statement on allergy and rhinology: rhinosinusitis 2021. Int Forum Allergy Rhinol [Internet]. 2021 Mar 14;11(3):213–739. Available from: https://onlinelibrary.wiley.com/doi/10.1002/alr.22741

76. Lane AP. The role of innate immunity in the pathogenesis of chronic rhinosinusitis. Curr Allergy Asthma Rep [Internet]. 2009 May 4;9(3):205–12. Available from:

http://link.springer.com/10.1007/s11882-009-0030-5

77. Michalik M, Krawczyk B. Chronic Rhinosinusitis—Microbiological Etiology, Potential Genetic Markers, and Diagnosis. Int J Mol Sci [Internet]. 2024 Mar 11;25(6):3201. Available from: https://www.mdpi.com/1422-0067/25/6/3201

78. Yip J, Monteiro E, Chan Y. Endotypes of chronic rhinosinusitis. Curr Opin Otolaryngol Head Neck Surg [Internet]. 2019 Feb;27(1):14–9. Available from: https://journals.lww.com/00020840-201902000-00004

79. Wang X, Sima Y, Zhao Y, Zhang N, Zheng M, Du K, et al. Endotypes of chronic rhinosinusitis based on inflammatory and remodeling factors. J Allergy Clin Immunol [Internet]. 2023 Feb;151(2):458–68. Available from: https://linkinghub.elsevier.com/retrieve/pii/S009167492201377X

80. Fujieda S, Imoto Y, Kato Y, Ninomiya T, Tokunaga T, Tsutsumiuchi T, et al. Eosinophilic chronic rhinosinusitis. Allergol Int [Internet]. 2019 Oct;68(4):403–12. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1323893019301030

81. Liu C, Wang K, Liu W, Zhang J, Fan Y, Sun Y. ALOX15+ M2 macrophages contribute to epithelial remodeling in eosinophilic chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol [Internet]. 2024 Sep;154(3):592–608. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0091674924004524

82. Carsuzaa F, Béquignon É, Dufour X, de Bonnecaze G, Lecron J-C, Favot L. Cytokine Signature and Involvement in Chronic Rhinosinusitis with Nasal Polyps. Int J Mol Sci [Internet]. 2021 Dec 30;23(1). Available from: http://www.ncbi.nlm.nih.gov/pubmed/35008843

83. Ji T, Li H. T-helper cells and their cytokines in pathogenesis and treatment of asthma. Front Immunol [Internet]. 2023 Jun 12;14. Available from: https://www.frontiersin.org/articles/10.3389/fimmu.2023.1149203/full

84. Cha H, Lim H-S, Park J-A, Jo A, Ryu HT, Kim DW, et al. Effects of Neutrophil and Eosinophil Extracellular Trap Formation on Refractoriness in Chronic Rhinosinusitis With Nasal Polyps. Allergy Asthma Immunol Res [Internet]. 2023;15(1):94. Available from: https://e-aair.org/DOIx.php?id=10.4168/aair.2023.15.1.94

85. Turner JH, Chandra RK, Li P, Bonnet K, Schlundt DG. Identification of clinically relevant chronic rhinosinusitis endotypes using cluster analysis of mucus cytokines. J Allergy Clin Immunol [Internet]. 2018 May;141(5):1895-1897.e7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0091674918302240

86. Stevens WW, Peters AT, Tan BK, Klingler AI, Poposki JA, Hulse KE, et al. Associations Between Inflammatory Endotypes and Clinical Presentations in Chronic Rhinosinusitis. J Allergy Clin Immunol Pract [Internet]. 2019 Nov;7(8):2812-2820.e3. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2213219819304647

87. Chapurin N, Wu J, Labby AB, Chandra RK, Chowdhury NI, Turner JH. Current insight into treatment of chronic rhinosinusitis: Phenotypes, endotypes, and implications for targeted therapeutics. J Allergy Clin Immunol [Internet]. 2022 Jul;150(1):22–32. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/35469844

88. Kato A, Peters AT, Stevens WW, Schleimer RP, Tan BK, Kern RC. Endotypes of chronic rhinosinusitis: Relationships to disease phenotypes, pathogenesis, clinical findings, and treatment approaches. Allergy [Internet]. 2022 Mar;77(3):812–26. Available from: http://www.ncbi.nlm.nih.gov/pubmed/34473358

89. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. Rhinology. 2012 Mar;50(1):1–12.

90. Hellings PW, Fokkens WJ, Orlandi R, Adriaensen GF, Alobid I, Baroody FM, et al. The EUFOREA pocket guide for chronic rhinosinusitis. Rhinol J [Internet]. 2022 Dec 1;0–0. Available from: https://www.rhinologyjournal.com/Abstract.php?id=3049

91. Aliberti S, Masefield S, Polverino E, De Soyza A, Loebinger MR, Menendez R, et al. Research priorities in bronchiectasis: A consensus statement from the EMBARC Clinical Research Collaboration. Eur Respir J [Internet]. 2016 Sep 1 [cited 2021 Mar 23];48(3):632–47. Available from: www.bronchiectasis.eu

92. Anwar GA, McDonnell MJ, Worthy SA, Bourke SC, Afolabi G, Lordan J, et al. Phenotyping adults with non-cystic fibrosis bronchiectasis: A prospective observational cohort study. Respir Med [Internet]. 2013 Jul;107(7):1001–7. Available from: http://dx.doi.org/10.1016/j.rmed.2013.04.013

93. Girón RM, de Gracia Roldán J, Olveira C, Vendrell M, Martínez-García MÁ, de la Rosa D, et al. Sex bias in diagnostic delay in bronchiectasis: An analysis of the Spanish Historical Registry of Bronchiectasis. Chron Respir Dis. 2017;14(4):360–9.

94. McDonnell MJ, Aliberti S, Goeminne PC, Restrepo MI, Finch S, Pesci A, et al. Comorbidities and the risk of mortality in patients with bronchiectasis: an international multicentre cohort study. Lancet Respir Med. 2016 Dec 1;4(12):969–79.

95. Aliberti S, Lonni S, Dore S, McDonnell MJ, Goeminne PC, Dimakou K, et al. Clinical phenotypes in adult patients with bronchiectasis. Eur Respir J [Internet]. 2016 Apr 1 [cited 2020 Jan 24];47(4):1113–22. Available from: http://erj.ersjournals.com/lookup/doi/10.1183/13993003.01899-2015

96. Mao B, Yang JW, Lu HW, Xu JF. Asthma and bronchiectasis exacerbation. Eur Respir J [Internet]. 2016;47(6):1680–6. Available from: http://dx.doi.org/10.1183/13993003.01862-2015

97. Clofent D, Álvarez A, Traversi L, Culebras M, Loor K, Polverino E. Comorbidities and mortality risk factors for patients with bronchiectasis. Expert Rev Respir Med [Internet]. 2021 May 4;15(5):623–34. Available from: https://pubmed.ncbi.nlm.nih.gov/33583300/

98. Guilemany JM, Mariño-Sánchez FS, Angrill J, Alobid I, Centellas S, Pujols L, et al. The importance of smell in patients with bronchiectasis. Respir Med. 2011 Jan;105(1):44–9.

99. Shteinberg M, Nassrallah N, Jrbashyan J, Uri N, Stein N AY. Upper airway involvement in bronchiectasis is marked by early age of onset and allergic features. In: ERJ Open Research 41 (2018): 00115-2017.

100. Shapiro AJ, Zariwala MA, Ferkol T, Davis SD, Sagel SD, Dell SD, et al. Diagnosis, monitoring, and treatment of primary ciliary dyskinesia: PCD foundation consensus recommendations based on state of the art review. Pediatr Pulmonol. 2016 Feb;51(2):115–32.

101. Ramakrishnan VR, Ferril GR, Suh JD, Woodson T, Green TJ, Kingdom TT. Upper and lower airways associations in patients with chronic rhinosinusitis and bronchiectasis. Int Forum Allergy Rhinol. 2013 Nov;3(11):921–7.

102. Ni Y, Shi G, Yu Y, Hao J, Chen T, Song H. Clinical characteristics of patients with chronic obstructive pulmonary disease with comorbid bronchiectasis: A systemic review and meta-analysis. Int J COPD [Internet]. 2015 Jul 28 [cited 2021 Mar 23];10(1):1465–75. Available from: https://pubmed.ncbi.nlm.nih.gov/26251586/

103. Du Q, Jin J, Liu X, Sun Y. Bronchiectasis as a Comorbidity of Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. Sethi S, editor. PLoS One [Internet]. 2016 Mar 15;11(3):e0150532. Available from: https://dx.plos.org/10.1371/journal.pone.0150532

104. Martínez-García MÁ, de la Rosa-Carrillo D, Soler-Cataluña JJ, Catalan-Serra P, Ballester M, Roca Vanaclocha Y, et al. Bronchial Infection and Temporal Evolution of Bronchiectasis in Patients With Chronic Obstructive Pulmonary Disease. Clin Infect Dis [Internet]. 2021 Feb 1;72(3):403–10. Available from: https://doi.org/10.1093/cid/ciaa069

105. Shi L, Wei F, Ma T, Zhou W, Li M, Wan Y. Impact of Radiographic Bronchiectasis in COPD. Respir Care [Internet]. 2020 Oct 1 [cited 2021 Jun 25];65(10):1561–73. Available from: https://pubmed.ncbi.nlm.nih.gov/32265292/

106. Oguzulgen IK, Kervan F, Ozis T, Turktas H. The impact of bronchiectasis in clinical presentation of asthma. South Med J [Internet]. 2007;100(5):468—471. Available from: https://doi.org/10.1097/SMJ.0b013e31802fa16f

107. Padilla-Galo A, Olveira C, Fernández de Rota-Garcia L, Marco-Galve I, Plata AJ, Alvarez A, et al. Factors associated with bronchiectasis in patients with uncontrolled asthma; the NOPES score: a study in 398 patients. Respir Res [Internet]. 2018 Dec 16;19(1):43. Available from: https://respiratory-research.biomedcentral.com/articles/10.1186/s12931-018-0746-7

108. Machado D, Pereira C, Teixeira L, Canelas A, Tavares B, Loureiro G, et al. Thoracic high resolution computed tomography (HRCT) in asthma. Eur Ann Allergy Clin Immunol. 2009 Oct;41(5):139–45.

109. Dimakou K, Gousiou A, Toumbis M, Kaponi M, Chrysikos S, Thanos L, et al. Investigation of bronchiectasis in severe uncontrolled asthma. Clin Respir J [Internet]. 2018 May 24;12(3):1212–8. Available from: https://doi.org/10.1111/crj.12653

110. Menzies D, Holmes L, Mccumesky G, Niven R. Aspergillus sensitization is associated with airflow limitation and bronchiectasis in severe asthma. Allergy [Internet]. 2011 Jan 25;66(5):679–85. Available from: https://doi.org/10.1111/j.1398-9995.2010.02542.x

111. Chalmers JD, Boersma W, Lonergan M, Jayaram L, Crichton ML, Karalus N, et al. Long-term macrolide antibiotics for the treatment of bronchiectasis in adults: an individual participant data meta-analysis. Lancet Respir Med [Internet]. 2019 Oct 1 [cited 2021 Jun 25];7(10):845–54. Available from:

https://pubmed.ncbi.nlm.nih.gov/31405828/

112. Pyarali FF, Schweitzer M, Bagley V, Salamo O, Guerrero A, Sharifi A, et al. Increasing Non-tuberculous Mycobacteria Infections in Veterans With COPD and Association With Increased Risk of Mortality. Front Med [Internet]. 2018 Nov 6 [cited 2021 Dec 15];5. Available from: https://pubmed.ncbi.nlm.nih.gov/30460238/

113. Andréjak C, Nielsen R, Thomsen VOØ, Duhaut P, Sørensen HT, Thomsen RW, et al. Chronic respiratory disease, inhaled corticosteroids and risk of non-tuberculous mycobacteriosis. Thorax. 2013 Mar;68(3):256–62.

114. Tejada S, Campogiani L, Solé-Lleonart C, Gómez A, Gallego M, Vendrell M, et al. Inhaled antibiotics for treatment of adults with non-cystic fibrosis bronchiectasis: A systematic review and meta-analysis. Eur J Intern Med [Internet]. 2021 [cited 2021 Jun 25]; Available from: https://pubmed.ncbi.nlm.nih.gov/33947626/

115. Cazzola M, Martínez-García MÁ, Matera MG. Bronchodilators in bronchiectasis: there is light but it is still too dim. Eur Respir J [Internet]. 2022 Jun 9;59(6):2103127. Available from: http://publications.ersnet.org/lookup/doi/10.1183/13993003.03127-2021

116. Jayaram L, Vandal AC, Chang CL, Lewis C, Tong C, Tuffery C, et al. Tiotropium treatment for bronchiectasis: a randomised, placebo-controlled, crossover trial. Eur Respir J [Internet]. 2022 Jun;59(6):2102184. Available from: http://publications.ersnet.org/lookup/doi/10.1183/13993003.02184-2021

117. Henkle E, Curtis JR, Chen L, Chan B, Aksamit TR, Daley CL, et al. Comparative risks of chronic inhaled corticosteroids and macrolides for bronchiectasis. Eur Respir J [Internet]. 2019 Jul 1 [cited 2021 Jun 25];54(1):1801896. Available from: https://doi.org/10.1183/13993003.01896-2018

118. Kapur N, Petsky HL, Bell S, Kolbe J, Chang AB. Inhaled corticosteroids for bronchiectasis. Cochrane Database Syst Rev [Internet]. 2018 May 16 [cited 2021 Jun 25];2018(5):CD000996. Available from: https://pubmed.ncbi.nlm.nih.gov/29766487/

119. Liu VX, Winthrop KL, Lu Y, Sharifi H, Nasiri HU, Ruoss SJ. Association between inhaled corticosteroid use and pulmonary nontuberculous mycobacterial infection. Ann Am Thorac Soc [Internet]. 2018 Oct 1 [cited 2021 Jun 25];15(10):1169–76. Available from: https://pubmed.ncbi.nlm.nih.gov/30213194/

120. Brode SK, Campitelli MA, Kwong JC, Lu H, Marchand-Austin A, Gershon AS, et al. The risk of mycobacterial infections associated with inhaled corticosteroid use. Eur Respir J [Internet]. 2017 Sep 20 [cited 2021 Dec 15];50(3):1700037. Available from: https://pubmed.ncbi.nlm.nih.gov/28931659/

121. Polverino E, De Soyza A, Dimakou K, Traversi L, Bossios A, Crichton ML, et al. The Association Between Bronchiectasis and Chronic Obstructive Pulmonary Disease: Data from the European Bronchiectasis Registry (EMBARC). Am J Respir Crit Care Med [Internet]. 2024 Jan 25;in press. Available from: https://www.atsjournals.org/doi/10.1164/rccm.202309-1614OC

122. Polverino E, Dimakou K, Traversi L, Bossios A, Haworth CS, Loebinger MR, et al. Bronchiectasis and asthma: Data from the European Bronchiectasis Registry (EMBARC). J Allergy Clin Immunol [Internet]. 2024 Feb;in press. Available from:

https://linkinghub.elsevier.com/retrieve/pii/S0091674924001891

123. Sims R, Kazda L, Michaleff ZA, Glasziou P, Thomas R. Consequences of health condition labelling: Protocol for a systematic scoping review [Internet]. Vol. 10, BMJ Open. BMJ Publishing Group; 2020 [cited 2021 Jul 2]. p. e037392. Available from: http://bmjopen.bmj.com/

124. Noble S, Bonner C, Hersch J, Jansen J, McGeechan K, McCaffery K. Could disease labelling have positive effects? An experimental study exploring the effect of the chronic fatigue syndrome label on intended social support. Patient Educ Couns. 2019 Mar 1;102(3):486–93.

125. Traversi L, Álvarez A, Polverino E. Bronchiectasis and Other Chronic Airway Diseases: A Clinical-based Approach. Barcelona Respir Netw [Internet]. 2022 Apr 7;8(1). Available from: https://www.brnreviews.com/frame_esp.php?id=207

126. Wenzel SE. Asthma: defining of the persistent adult phenotypes. Lancet. 2006;368(9537):804–13.

127. Green RH, Brightling CE, Woltmann G, Parker D, Wardlaw AJ, Pavord ID. Analysis of induced sputum in adults with asthma: identification of subgroup with isolated sputum neutrophilia and poor response to inhaled corticosteroids. Thorax. 2002 Oct;57(10):875–9.

128. Coman I, Pola-Bibián B, Barranco P, Vila-Nadal G, Dominguez-Ortega J, Romero D, et al. Bronchiectasis in severe asthma. Ann Allergy, Asthma Immunol [Internet]. 2018 Apr;120(4):409–13. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1081120618301431

129. De Angelis A, Johnson ED, Sutharsan S, Aliberti S. Exacerbations of bronchiectasis. Eur Respir Rev [Internet]. 2024 Jul 24;33(173):240085. Available from: https://publications.ersnet.org/lookup/doi/10.1183/16000617.0085-2024

130. Hill AT, Haworth CS, Aliberti S, Barker A, Blasi F, Boersma W, et al. Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research. Eur Respir J [Internet]. 2017 Jun;49(6). Available from: http://dx.doi.org/10.1183/13993003.00051-2017

131. Máiz Carro L, Martínez-García MA. Nebulized hypertonic saline in noncystic fibrosis bronchiectasis: a comprehensive review. Ther Adv Respir Dis [Internet]. 2019 Jan 8;13. Available from: https://journals.sagepub.com/doi/10.1177/1753466619866102

132. Radovanovic D, Santus P, Blasi F, Sotgiu G, D'Arcangelo F, Simonetta E, et al. A comprehensive approach to lung function in bronchiectasis. Respir Med [Internet]. 2018 Dec;145:120–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0954611118303597

133. Guan W-J, Gao Y-H, Xu G, Li H-M, Yuan J-J, Zheng J-P, et al. Bronchodilator response in adults with bronchiectasis: correlation with clinical parameters and prognostic implications. J Thorac Dis [Internet]. 2016 Jan;8(1):14–23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26904207

134. Sevgili S, Hasanoğlu HC, Karalezli A, Er M. [Bronchial reversibility in the patients with bronchiectasis]. Tuberk Toraks [Internet]. 2009;57(1):38–47. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19533436

135. Tan C, Ma D, Wang K, Tu C, Chen M, Zheng X, et al. The Role of Impulse Oscillometry in Evaluating Disease Severity and Predicting the Airway Reversibility in Patients With Bronchiectasis. Front Med

[Internet]. 2022 Feb 25;9:796809. Available from: https://www.frontiersin.org/articles/10.3389/fmed.2022.796809/full

136. Gilley SK, Stenbit AE, Pasek RC, Sas KM, Steele SL, Amria M, et al. Deletion of airway cilia results in noninflammatory bronchiectasis and hyperreactive airways. Am J Physiol Cell Mol Physiol [Internet]. 2014 Jan 15;306(2):L162–9. Available from: https://www.physiology.org/doi/10.1152/ajplung.00095.2013

137. Varpela E, Laitinen LA, Keskinen H, Korhola O. Asthma, allergy and bronchial hyper-reactivity to histamine in patients with bronchiectasis. Clin Allergy. 1978 May;8(3):273–80.

138. Bahous J, Cartier A, Pineau L, Bernard C, Ghezzo H, Martin RR, et al. Pulmonary function tests and airway responsiveness to methacholine in chronic bronchiectasis of the adult. Bull Eur Physiopathol Respir. 1984;20(4):375–80.

139. Lonni S, Chalmers JD, Goeminne PC, McDonnell MJ, Dimakou K, De Soyza A, et al. Etiology of Non-Cystic Fibrosis Bronchiectasis in Adults and Its Correlation to Disease Severity. Ann Am Thorac Soc. 2015 Dec;12(12):1764–70.

140. Olveira C, Padilla A, Martínez-García M-Á, de la Rosa D, Girón R-M, Vendrell M, et al. Etiología de las bronquiectasias en una cohorte de 2.047 pacientes. Análisis del registro histórico español. Arch Bronconeumol [Internet]. 2017 Jul;53(7):366–74. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0300289616303520

141. Mäntylä J, Mazur W, Törölä T, Bergman P, Saarinen T, Kauppi P. Asthma as aetiology of bronchiectasis in Finland. Respir Med [Internet]. 2019 Jun;152:105–11. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0954611119301507

142. Olveira C, Padilla A, Martinez-Garcia M-A, de la Rosa D, Giron R-M, Vendrell M, et al. Etiology of Bronchiectasis in a Cohort of 2047 Patients. An Analysis of the Spanish Historical Bronchiectasis Registry. Arch Bronconeumol. 2017 Jul;53(7):366–74.

143. Kadowaki T, Yano S, Wakabayashi K, Kobayashi K, Ishikawa S, Kimura M, et al. An analysis of etiology, causal pathogens, imaging patterns, and treatment of Japanese patients with bronchiectasis. Respir Investig [Internet]. 2015 Jan;53(1):37–44. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2212534514001075

144. Aksamit TR, O'Donnell AE, Barker A, Olivier KN, Winthrop KL, Daniels MLA, et al. Adult Patients With Bronchiectasis. Chest [Internet]. 2017 May;151(5):982–92. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0012369216623541

145. Dhar R, Singh S, Talwar D, Murali Mohan B V., Tripathi SK, Swarnakar R, et al. Clinical outcomes of bronchiectasis in India: data from the EMBARC/Respiratory Research Network of India registry. Eur Respir J. 2023 Jan;61.

146. Moon SM, Choi H, Kang HK, Lee SW, Sim YS, Park HY, et al. Impacts of Asthma in Patients With Bronchiectasis: Findings From the KMBARC Registry. Allergy Asthma Immunol Res [Internet]. 2023;15(1):83. Available from: https://e-aair.org/DOIx.php?id=10.4168/aair.2023.15.1.83

147. Xu J-F, Zheng H-Z, Lu H-W, Wang L-W, Wu B, Lv X-D, et al. Baseline characteristics of patients in the

Chinese Bronchiectasis Registry (BE-China): a multicentre prospective cohort study. Lancet Respir Med. 2025 Jan;

148. Paganin F, Trussard V, Seneterre E, Chanez P, Giron J, Godard P, et al. Chest Radiography and High Resolution Computed Tomography of the Lungs in Asthma. Am Rev Respir Dis [Internet]. 1992 Oct;146(4):1084–7. Available from: http://www.atsjournals.org/doi/abs/10.1164/ajrccm/146.4.1084

149. Frøssing L, Von Bülow A, Porsbjerg C. Bronchiectasis in severe asthma is associated with eosinophilic airway inflammation and activation. J Allergy Clin Immunol Glob [Internet]. 2023 Feb;2(1):36–42. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2772829322000935

150. Gupta S, Siddiqui S, Haldar P, Raj JV, Entwisle JJ, Wardlaw AJ, et al. Qualitative analysis of high-resolution CT scans in severe asthma. Chest. 2009;136(6):1521–8.

151. Dimakou K, Toumbis M, Tsikritsaki, K; Malagari, K; Liapikou, A; Kaponi M. Bronchiectasis in severe uncontrolled asthma. Vol. 70, Thorax. 2015. p. A109–10.

152. Kim S, Nam Jin K, Cho SH, Hyun Lee C, Kang HR. Severe Asthma Phenotypes Classified by Site of Airway Involvement and Remodeling via Chest CT Scan. J Investig Allergol Clin Immunol [Internet]. 2018 Apr;28(5):0. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29667580

153. Heffler E, Blasi F, Latorre M, Menzella F, Paggiaro P, Pelaia G, et al. The Severe Asthma Network in Italy: Findings and Perspectives. J Allergy Clin Immunol Pract [Internet]. 2019 May;7(5):1462–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2213219818306731

154. García-Clemente M, Enríquez-Rodríguez AI, Iscar-Urrutia M, Escobar-Mallada B, Arias-Guillén M, López-González FJ, et al. Severe asthma and bronchiectasis. J Asthma [Internet]. 2020 May 3;57(5):505–9. Available from: https://www.tandfonline.com/doi/full/10.1080/02770903.2019.1579832

155. Paganin F, Séneterre E, Chanez P, P Daurés J, Bruel J, B Michel F, et al. Computed tomography of the lungs in asthma: Influence of disease severity and etiology. Vol. 153, American journal of respiratory and critical care medicine. 1996. 110–114 p.

156. Grenier P, Mourey-Gerosa I, Benali K, Brauner MW, Leung AN, Lenoir S, et al. Abnormalities of the airways and lung parenchyma in asthmatics: CT observations in 50 patients and inter- and intraobserver variability. Eur Radiol. 1996;6(2):199–206.

157. Park JW, Hong YK, Kim CW, Kim DK, Choe KO, Hong CS. High-resolution computed tomography in patients with bronchial asthma: correlation with clinical features, pulmonary functions and bronchial hyperresponsiveness. J Investig Allergol Clin Immunol. 1997;7(3):186–92.

158. Coman I, Pola-Bibián B, Barranco P, Vila-Nadal G, Dominguez-Ortega J, Romero D, et al. Bronchiectasis in severe asthma: Clinical features and outcomes. Ann Allergy, Asthma Immunol [Internet]. 2018;120(4):409–13. Available from: https://doi.org/10.1016/j.anai.2018.02.016

159. Kang HR, Choi GS, Park SJ, Song YK, Kim JM, Ha J, et al. The effects of bronchiectasis on asthma exacerbation. Tuberc Respir Dis (Seoul). 2014;77(5):209–14.

160. Luján M, Gallardo X, Amengual MJ, Bosque M, Mirapeix RM, Domingo C. Prevalence of Bronchiectasis in Asthma according to Oral Steroid Requirement: Influence of Immunoglobulin Levels.

Biomed Res Int. 2013;2013:1–7.

161. Kurt E, Ozkan R, Orman A, Calisir C, Metintas M. Irreversiblity of Remodeled Features on High-Resolution Computerized Tomography Scans of Asthmatic Patients on Conventional Therapy: A 6-Year Longitudinal Study. J Asthma [Internet]. 2009 Jan 2;46(3):300–7. Available from: http://www.tandfonline.com/doi/full/10.1080/02770900902718837

162. Cukier A, Stelmach R, Kavakama JI, Terra Filho M, Vargas F. Persistent asthma in adults: comparison of high resolution computed tomography of the lungs after one year of follow-up. Rev Hosp Clin Fac Med Sao Paulo [Internet]. 2001 Jun;56(3):63–8. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0041-87812001000300001&lng=en&tlng=en

163. Takemura M, Niimi A, Minakuchi M, Matsumoto H, Ueda T, Chin K, et al. Bronchial Dilatation in Asthma. Chest [Internet]. 2004 Apr;125(4):1352–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0012369215320961

164. Bisaccioni C, Aun MV, Cajuela E, Kalil J, Agondi RC, Giavina-Bianchi P. Comorbidities in severe asthma: frequency of rhinitis, nasal polyposis, gastroesophageal reflux disease, vocal cord dysfunction and bronchiectasis. Clinics [Internet]. 2009;64(8):769–73. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1807-59322009000800010&lng=en&nrm=iso&tlng=en

165. Luján M, Gallardo X, Amengual MJ, Bosque M, Mirapeix RM, Domingo C. Prevalence of bronchiectasis in asthma according to oral steroid requirement: Influence of immunoglobulin levels. Biomed Res Int. 2013;2013.

166. Dimakou K, Gousiou A, Toumbis M, Kaponi M, Chrysikos S, Thanos L, et al. Investigation of bronchiectasis in severe uncontrolled asthma. Clin Respir J. 2018 Mar;12(3):1212–8.

167. Henkle E, Aksamit TR, Barker AF, Curtis JR, Daley CL, Anne Daniels ML, et al. Pharmacotherapy for Non-Cystic Fibrosis Bronchiectasis: Results From an NTM Info & Research Patient Survey and the Bronchiectasis and NTM Research Registry. Chest. 2017;152(6):1120–7.

168. Weatherburn CJ, Guthrie B, Mercer SW, Morales DR. Comorbidities in adults with asthma: Population-based cross-sectional analysis of 1.4 million adults in Scotland. Clin Exp Allergy. 2017;47(10):1246–52.

169. Xie H, Chen P, Liu L. Analysis of bronchiectasis in hospitalized asthmatic patients: 10-year experience of a single center. Zhonghua Yi Xue Za Zhi. 2019 Apr;99:1210–5.

170. Dupin C, Marchand-Adam S, Favelle O, Costes R, Gatault P, Diot P, et al. Asthma and Hypogammaglobulinemia: an Asthma Phenotype with Low Type 2 Inflammation. J Clin Immunol. 2016 Nov;36(8):810–7.

171. Halpin DMG, Criner GJ, Papi A, Singh D, Anzueto A, Martinez FJ, et al. Global Initiative for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease. The 2020 GOLD Science Committee Report on COVID-19 and Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med [Internet]. 2021 Jan 1 [cited 2021 Dec 24];203(1):24–36. Available from: https://pubmed.ncbi.nlm.nih.gov/33146552/

172. Aliberti S, Goeminne PC, O'Donnell AE, Aksamit TR, Al-Jahdali H, Barker AF, et al. Criteria and definitions for the radiological and clinical diagnosis of bronchiectasis in adults for use in clinical trials: international consensus recommendations. Lancet Respir Med [Internet]. 2021 Sep [cited 2021 Nov 3];0(0). Available from: http://www.thelancet.com/article/S2213260021002770/fulltext

173. Chalmers JD, Goeminne P, Aliberti S, McDonnell MJ, Lonni S, Davidson J, et al. The bronchiectasis severity index an international derivation and validation study. Am J Respir Crit Care Med. 2014;

174. Martínez-García MA, Perpiñá-Tordera M, Soler-Cataluña JJ, Román-Sánchez P, Lloris-Bayo A, González-Molina A. Dissociation of lung function, dyspnea ratings and pulmonary extension in bronchiectasis. Respir Med. 2007 Nov;101(11):2248–53.

175. 2025 GOLD Report - Global Initiative for Chronic Obstructive Lung Disease - GOLD. https://goldcopd.org/2025-gold-report/.

176. de la Rosa-Carrillo D, de Granda-Orive JI, Diab Cáceres L, Gutiérrez Pereyra F, Raboso Moreno B, Martínez-García MÁ, et al. The impact of smoking on bronchiectasis and its comorbidities [Internet]. Vol. 18, Expert Review of Respiratory Medicine. Taylor and Francis Ltd.; 2024. p. 255–68. Available from: https://www.tandfonline.com/doi/full/10.1080/17476348.2024.2369716

177. Wang K, Liao Y, Li X, Wang R, Zeng Z, Cheng M, et al. Inhibition of neutrophil elastase prevents cigarette smoke exposure-induced formation of neutrophil extracellular traps and improves lung function in a mouse model of chronic obstructive pulmonary disease. Int Immunopharmacol. 2023 Jan;114.

178. Huang JT-J, Cant E, Keir HR, Barton AK, Kuzmanova E, Shuttleworth M, et al. Endotyping COPD, Bronchiectasis and the 'COPD-bronchiectasis Association'. Am J Respir Crit Care Med [Internet]. 2022 Apr 18 [cited 2022 May 30]; Available from: https://pubmed.ncbi.nlm.nih.gov/35436182/

179. Chen YF, Hou HH, Chien N, Lu KZ, Lin CH, Liao YC, et al. The clinical impacts of lung microbiome in bronchiectasis with fixed airflow obstruction: a prospective cohort study. Respir Res. 2024 Dec;25.

180. Tan WC, Hague CJ, Leipsic J, Bourbeau J, Zheng L, Li PZ, et al. Findings on Thoracic Computed Tomography Scans and Respiratory Outcomes in Persons with and without Chronic Obstructive Pulmonary Disease: A Population-Based Cohort Study. Kostikas K, editor. PLoS One [Internet]. 2016 Nov 18;11(11):e0166745. Available from: https://dx.plos.org/10.1371/journal.pone.0166745

181. Monteagudo M, Rodríguez-Blanco T, Barrecheguren M, Simonet P, Miravitlles M. Prevalence and incidence of bronchiectasis in Catalonia, Spain: A population-based study. Respir Med [Internet]. 2016 Dec;121:26–31. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0954611116302670

182. Diaz AA, Young TP, Maselli DJ, Martinez CH, Maclean ES, Yen A, et al. Bronchoarterial ratio in never-smokers adults: Implications for bronchial dilation definition. Respirology. 2017 Jan 1;22(1):108–13.

183. Diaz AA, Young TP, Maselli DJ, Martinez CH, Gill R, Nardelli P, et al. Quantitative CT Measures of Bronchiectasis in Smokers. Chest [Internet]. 2017 Jun 1 [cited 2020 Jan 6];151(6):1255–62. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0012369216624601

184. Martinez-Garcia MA, Miravitlles M. Bronchiectasis in COPD patients: more than a comorbidity? Int J

Chron Obstruct Pulmon Dis [Internet]. 2017 May;Volume 12:1401–11. Available from: https://www.dovepress.com/bronchiectasis-in-copd-patients-more-than-a-comorbidity-peer-reviewed-article-COPD

185. De la Rosa D, Martínez-Garcia M-A, Giron RM, Vendrell M, Olveira C, Borderias L, et al. Clinical impact of chronic obstructive pulmonary disease on non-cystic fibrosis bronchiectasis. A study on 1,790 patients from the Spanish Bronchiectasis Historical Registry. Chotirmall SH, editor. PLoS One [Internet]. 2017 May 18;12(5):e0177931. Available from: https://dx.plos.org/10.1371/journal.pone.0177931

186. Kim SH, Kim C, Jeong I, Lee SJ, Kim TH, Lee CY, et al. Chronic Obstructive Pulmonary Disease Is Associated With Decreased Quality of Life in Bronchiectasis Patients: Findings From the KMBARC Registry. Front Med [Internet]. 2021 Aug 16;8. Available from: https://www.frontiersin.org/articles/10.3389/fmed.2021.722124/full

187. Dhar R, Singh S, Talwar D, Mohan M, Tripathi SK, Swarnakar R, et al. Bronchiectasis in India: results from the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) and Respiratory Research Network of India Registry. Lancet Glob Heal [Internet]. 2019 Sep;7(9):e1269–79. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2214109X19303274

188. Xu J-F, Zheng H-Z, Lu H-W, Wang L-W, Wu B, Lv X-D, et al. Baseline characteristics of patients in the Chinese Bronchiectasis Registry (BE-China): a multicentre prospective cohort study. Lancet Respir Med [Internet]. 2025 Feb;13(2):166–76. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2213260024003643

189. da Silva SMD, Moreira MM, Paschoal IA, Pereira MC. Bronchiectasis associated with severe COPD: Clinical, functional, microbiological and tomographic features. Lung India. 2022;39:502–9.

190. Lu H-Y, Liao K-M. The incidence of bronchiectasis in chronic obstructive pulmonary disease. Open Med (Warsaw, Poland). 2022;17:1927–34.

191. Deghdegh K, Boukadoum N, Terra B, Amoura K, Benali R. Characteristics of Bronchiectasis Associated with Chronic Obstructive Pulmonary Disease. Open Respir Med J [Internet]. 2022 May 31;16(1). Available from: https://openrespiratorymedicinejournal.com/VOLUME/16/ELOCATOR/e187430642203311/

192. Seo H, Sim YS, Min KH, Lee JH, Kim BK, Oh YM, et al. The Relationship Between Comorbidities and Microbiologic Findings in Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease. Int J COPD. 2022;17:855–67.

193. Dai Z, Zhong Y, Cui Y, Ma Y, Zeng H, Chen Y. Analysis of clinical characteristics, prognosis and influencing factors in patients with bronchiectasis-chronic obstructive pulmonary disease overlap syndrome: A prospective study for more than five years. J Glob Health [Internet]. 2024 Jun 28;14:04129. Available from: https://jogh.org/2024/jogh-14-04129

194. Júnior JFN, Hermann DR, dos ReisAmérico R, Filho ISB, Stamm AEC, Pignatari SSN. A brief history of otorhinolaryngolgy: otology, laryngology and rhinology. Braz J Otorhinolaryngol [Internet]. 2007 Sep;73(5):693–703. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1808869415301324

195. Bachert C, Luong AU, Gevaert P, Mullol J, Smith SG, Silver J, et al. The Unified Airway Hypothesis: Evidence From Specific Intervention With Anti–IL-5 Biologic Therapy. J Allergy Clin Immunol Pract [Internet]. 2023 Sep;11(9):2630–41. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2213219823005470

196. Grossman J. One Airway, One Disease. Chest [Internet]. 1997 Feb;111(2):11S-16S. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0012369215435056

197. Morgan LC, Birman CS. The impact of Primary Ciliary Dyskinesia on the upper respiratory tract. Paediatr Respir Rev [Internet]. 2016 Mar;18:33–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1526054215000913

198. Hamilos DL. Chronic Rhinosinusitis in Patients with Cystic Fibrosis. J Allergy Clin Immunol Pract [Internet]. 2016 Jul;4(4):605–12. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2213219816301234

199. Shteinberg M, Nassrallah N, Jrbashyan J, Uri N, Stein N, Adir Y. Bronchiectasis with upper airways symptoms is associated with allergic features and frequent exacerbations. In: 1st World Bronchiectasis Conference Hannover. 2016.

200. Yu I, Yong SJ, Lee WY, Kim SH, Lee H, Na JO, et al. Prevalence of chronic rhinosinusitis and its relating factors in patients with bronchiectasis: findings from KMBARC registry. Korean J Intern Med. 2022 Sep;37:1002–10.

201. Shteinberg M, Chalmers JD, Narayana JK, Dicker AJ, Rahat MA, Simanovitch E, et al. Bronchiectasis with Chronic Rhinosinusitis Is Associated with Eosinophilic Airway Inflammation and Is Distinct from Asthma. Ann Am Thorac Soc [Internet]. 2024 May;21(5):748–58. Available from: https://www.atsjournals.org/doi/10.1513/AnnalsATS.202306-551OC

202. Benninger M, Ferguson B, Hadley J, Hamilos D, Jacobs M, Kennedy D, et al. Adult chronic rhinosinusitis: Definitions, diagnosis, epidemiology, and pathophysiology. Otolaryngol - Head Neck Surg. 2003;129(3):S1–32.

203. Shirahata Y. [Correlation between upper airway tract and lower airway tract in the break down of sinobronchiectasis]. Nihon Jibiinkoka Gakkai Kaiho. 1990 Dec;93(12):1991–8.

204. Guan W, Gao Y, Li H, Yuan J, Chen R, Zhong N. Impacts of Co-Existing Chronic Rhinosinusitis on Disease Severity and Risks of Exacerbations in Chinese Adults with Bronchiectasis. PLoS One. 2015;10(9):e0137348.

205. Guilemany JM, Angrill J, Alobid I, Centellas S, Prades E, Roca J, et al. United airways: The impact of chronic rhinosinusitis and nasal polyps in bronchiectasic patient's quality of life. Allergy Eur J Allergy Clin Immunol. 2009;

206. Handley E, Nicolson CH, Hew M, Lee AL. Prevalence and Clinical Implications of Chronic Rhinosinusitis in People with Bronchiectasis: A Systematic Review. J Allergy Clin Immunol Pract. 2019 Jul;7:2004-2012.e1.

207. Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, et al. Executive summary of EPOS 2020 including integrated care pathways. Rhinology. 2020;58(2):82–111.

208. Guilemany JM, Alobid I, Angrill J, Ballesteros F, Bernal-Sprekelsen M, Picado C, et al. The impact of bronchiectasis associated to sinonasal disease on quality of life. Respir Med. 2006 Nov;100(11):1997–2003.

209. Shteinberg M, Goeminne P, Loebinger M, Haworth C, Ringshausen F, Dimakou K, et al. Rhinosinusitis is associated with increased symptoms and more frequent exacerbations among patients with bronchiectasis- data from the EMBARC registry. In: Respiratory infections [Internet]. European Respiratory Society; 2018. p. PA350. Available from: https://publications.ersnet.org/lookup/doi/10.1183/13993003.congress-2018.PA350

210. Wang Y, Yang H-B. Effects of functional endoscopic sinus surgery on the treatment of bronchiectasis combined with chronic rhino-sinusitis. Acta Otolaryngol. 2016 Aug;136(8):860–3.

211. Alanin MC, Aanaes K, Høiby N, Pressler T, Skov M, Nielsen KG, et al. Sinus surgery can improve quality of life, lung infections, and lung function in patients with primary ciliary dyskinesia. Int Forum Allergy Rhinol. 2017 Mar;7(3):240–7.

212. Wallwork B, Coman W, Mackay-Sim A, Greiff L, Cervin A. A double-blind, randomized, placebo-controlled trial of macrolide in the treatment of chronic rhinosinusitis. Laryngoscope. 2006 Feb;116(2):189–93.

213. Haxel BR, Clemens M, Karaiskaki N, Dippold U, Kettern L, Mann WJ. Controlled trial for long-term low-dose erythromycin after sinus surgery for chronic rhinosinusitis. Laryngoscope. 2015 May;125(5):1048–55.

214. Lees KA, Orlandi RR, Oakley G, Alt JA. The Role of Macrolides and Doxycycline in Chronic Rhinosinusitis. Immunol Allergy Clin North Am [Internet]. 2020 May;40(2):303–15. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0889856119300967

215. Videler WJ, Badia L, Harvey RJ, Gane S, Georgalas C, van der Meulen FW, et al. Lack of efficacy of long-term, low-dose azithromycin in chronic rhinosinusitis: a randomized controlled trial. Allergy. 2011 Nov;66(11):1457–68.

216. Schwartz BS, Al-Sayouri SA, Pollak JS, Hirsch AG, Kern R, Tan B, et al. Strong and consistent associations of precedent chronic rhinosinusitis with risk of non–cystic fibrosis bronchiectasis. J Allergy Clin Immunol. 2022 Sep;150:701-708.e4.

217. Murphy MK, Black NA, Lamping DL, McKee CM, Sanderson C, Askham J, et al. Consensus development methods, and their use in clinical guideline development. Health Technol Assess (Rockv) [Internet]. 1998 [cited 2019 Dec 17];2(3). Available from: https://www.journalslibrary.nihr.ac.uk/hta/hta2030

218. Traversi L, Miravitlles M, Martinez-Garcia MA, Shteinberg M, Bossios A, Dimakou K, et al. ROSE: radiology, obstruction, symptoms and exposure – a Delphi consensus definition of the association of COPD and bronchiectasis by the EMBARC Airways Working Group. ERJ Open Res [Internet]. 2021 Oct [cited 2021 Dec 15];7(4):00399–2021. Available from: https://doi.org/10.1183/23120541.00399-2021

219. Dolliver W, Wang W, Orejas J, Maselli D, Yen A, Young K, et al. The ROSE criteria for coexistent

COPD-bronchiectasis: association with future exacerbations and death. In: 1001 - Respiratory infections and bronchiectasis [Internet]. European Respiratory Society; 2022. p. 2550. Available from: https://publications.ersnet.org/lookup/doi/10.1183/13993003.congress-2022.2550

220. Chen Y-F, Chang C-L, Hou H-H, Chien N, Lu K-Z, Chen Y-Y, et al. The impact of COPD–bronchiectasis association on clinical outcomes: insights from East Asian cohorts validating the ROSE criteria. ERJ Open Res [Internet]. 2025 Mar 11;11(2):00626–2024. Available from: https://publications.ersnet.org/lookup/doi/10.1183/23120541.00626-2024

221. Huang JT-J, Cant E, Keir HR, Barton AK, Kuzmanova E, Shuttleworth M, et al. Endotyping Chronic Obstructive Pulmonary Disease, Bronchiectasis, and the "Chronic Obstructive Pulmonary Disease–Bronchiectasis Association". Am J Respir Crit Care Med [Internet]. 2022 Aug 15;206(4):417–26. Available from: https://www.atsjournals.org/doi/10.1164/rccm.202108-1943OC

222. Díaz AA, Nardelli P, Wang W, San José Estépar R, Yen A, Kligerman S, et al. Artificial Intelligence–based CT Assessment of Bronchiectasis: The COPDGene Study. Radiology [Internet]. 2023 Apr 1;307(1). Available from: http://pubs.rsna.org/doi/10.1148/radiol.221109

223. Diaz AA, Wang W, Orejas JL, Elalami R, Dolliver WR, Nardelli P, et al. Suspected Bronchiectasis and Mortality in Adults With a History of Smoking Who Have Normal and Impaired Lung Function. Ann Intern Med [Internet]. 2023 Oct;176(10):1340–8. Available from: https://www.acpjournals.org/doi/10.7326/M23-1125

224. Ringshausen FC, Baumann I, de Roux A, Dettmer S, Diel R, Eichinger M, et al. Management erwachsener Patientinnen und Patienten mit Bronchiektasen-Erkrankung. Pneumologie. 2024 Nov;78:833–99.

225. Pan C, He Z, Lin S, Yue J, Chen Z, Guan W. Clinical Characteristics and Outcomes of the Phenotypes of COPD-Bronchiectasis Association. Arch Bronconeumol [Internet]. 2024 Jun;60(6):356–63. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0300289624001108

226. Chen Y-F, Hou H-H, Chien N, Lu K-Z, Lin C-H, Liao Y-C, et al. The clinical impacts of lung microbiome in bronchiectasis with fixed airflow obstruction [Internet]. 2024. Available from: https://www.researchsquare.com/article/rs-3825568/v1

227. Chalmers JD, Polverino E, Crichton ML, Ringshausen FC, De Soyza A, Vendrell M, et al. Bronchiectasis in Europe: data on disease characteristics from the European Bronchiectasis registry (EMBARC). Lancet Respir Med [Internet]. 2023 Jul;11(7):637–49. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2213260023000930

228. Chalmers JD, Aliberti S, Polverino E, Vendrell M, Crichton M, Loebinger M, et al. The EMBARC European Bronchiectasis Registry: protocol for an international observational study. ERJ Open Res. 2016;2(1):00081-2015-81–2015.

229. Pasteur M, Bilton D, Hill AT, on behalf of the British Thoracic Society Bronchiectasis (non-CF) Guideline Group. British Thoracic Society Guideline for non-CFbronchiectasis. Thorax. 2010;65(1):1–58.

230. No Title. Available from: https://goldcopd.org/2025-gold-report/

231. Alif SM, Dharmage SC, Bowatte G, Karahalios A, Benke G, Dennekamp M, et al. Occupational exposure and risk of chronic obstructive pulmonary disease: a systematic review and meta-analysis. Expert Rev Respir Med [Internet]. 2016 Aug 2;10(8):861–72. Available from: http://www.tandfonline.com/doi/full/10.1080/17476348.2016.1190274

232. Fishwick D, Sen D, Barber C, Bradshaw L, Robinson E, Sumner J. Occupational chronic obstructive pulmonary disease: a standard of care. Occup Med (Chic Ill) [Internet]. 2015 Jun;65(4):270–82. Available from: https://academic.oup.com/occmed/article-lookup/doi/10.1093/occmed/kqv019

233. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. Respir Med. 1991 Sep;85 Suppl B:25–7.

234. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, et al. Series 'ATS/ERS Task Force: Standardisation of Lung Function Testing' Standardisation of spirometry. Eur Respir J. 2005;

235. Checkley AM, Chiodini PL, Dockrell DH, Bates I, Thwaites GE, Booth HL, et al. Eosinophilia in returning travellers and migrants from the tropics: UK recommendations for investigation and initial management. J Infect. 2010 Jan;60(1):1–20.

236. American Thoracic Society (ATS); European Respiratory Society (ERS). ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. Am J Respir Crit Care Med. 2005 Apr;171(8):912–30.

237. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med. 2011 Sep;184(5):602–15.

238. Chen F-J, Liao H, Huang X-Y, Xie C-M. Importance of fractional exhaled nitric oxide in diagnosis of bronchiectasis accompanied with bronchial asthma. J Thorac Dis. 2016 May;8(5):992–9.

239. DeConde AS, Mace JC, Bodner T, Hwang PH, Rudmik L, Soler ZM, et al. SNOT-22 quality of life domains differentially predict treatment modality selection in chronic rhinosinusitis. Int Forum Allergy Rhinol [Internet]. 2014 Dec;4(12):972–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25323055

240. Wittgenstein L. Tractatus Logico-Philosophicus. Ogden CK, editor. London: Routledge & Kegan Paul.; 1922.

241. Miravitlles M. Asthma-COPD Overlap (ACO) PRO-CON Debate. ACO: Call Me by My Name. COPD J Chronic Obstr Pulm Dis [Internet]. 2020 Sep 2;17(5):471–3. Available from: https://www.tandfonline.com/doi/full/10.1080/15412555.2020.1817883

242. Papi A. Asthma COPD Overlap PRO-CON Debate. ACO: The Mistaken Term. COPD J Chronic Obstr Pulm Dis [Internet]. 2020 Sep 2;17(5):474–6. Available from: https://www.tandfonline.com/doi/full/10.1080/15412555.2020.1817882

243. Glass D, Kelsall H, Slegers C, Forbes A, Loff B, Zion D, et al. A telephone survey of factors affecting willingness to participate in health research surveys. BMC Public Health [Internet]. 2015 Dec 5;15(1):1017. Available from: http://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-015-2350-9

244. Markanday S, Brennan SL, Gould H, Pasco JA. Sex-differences in reasons for non-participation at recruitment: Geelong Osteoporosis Study. BMC Res Notes [Internet]. 2013 Dec 18;6(1):104. Available from: https://bmcresnotes.biomedcentral.com/articles/10.1186/1756-0500-6-104

245. Spinou A, Almagro M, Harris B, Boyd J, Berg T, Herrero-Cortina B, et al. Diagnostic delay and access to care in bronchiectasis: data from the EMBARC/ELF patient survey. Eur Respir J [Internet]. 2024 Jul;64(1):2301504. Available from: https://publications.ersnet.org/lookup/doi/10.1183/13993003.01504-2023

246. Aliberti S, Ringshausen FC, Dhar R, Haworth CS, Loebinger MR, Dimakou K, et al. Objective sputum colour assessment and clinical outcomes in bronchiectasis: data from the European Bronchiectasis Registry (EMBARC). Eur Respir J [Internet]. 2024 Apr;63(4):2301554. Available from: https://publications.ersnet.org/lookup/doi/10.1183/13993003.01554-2023

247. Panagioti M, Richardson G, Small N, Murray E, Rogers A, Kennedy A, et al. Self-management support interventions to reduce health care utilisation without compromising outcomes: a systematic review and meta-analysis. BMC Health Serv Res [Internet]. 2014 Dec 27;14(1):356. Available from: https://bmchealthservres.biomedcentral.com/articles/10.1186/1472-6963-14-356

248. Lenferink A, Brusse-Keizer M, van der Valk PD, Frith PA, Zwerink M, Monninkhof EM, et al. Self-management interventions including action plans for exacerbations versus usual care in patients with chronic obstructive pulmonary disease. Cochrane Database Syst Rev [Internet]. 2017 Aug 4;2017(8). Available from: http://doi.wiley.com/10.1002/14651858.CD011682.pub2

249. Murray MP, Turnbull K, MacQuarrie S, Pentland JL, Hill AT. Validation of the Leicester Cough Questionnaire in non-cystic fibrosis bronchiectasis. Eur Respir J. 2009 Jul;34:125–31.

250. Spinou A, Lee KK, Sinha A, Elston C, Loebinger MR, Wilson R, et al. The Objective Assessment of Cough Frequency in Bronchiectasis. Lung [Internet]. 2017 Oct 13;195(5):575–85. Available from: http://link.springer.com/10.1007/s00408-017-0038-x

251. Muñoz G, Buxó M, De Gracia J, Olveira C, Martinez-Garcia MA, Giron R, et al. Validation of a Spanish version of the Leicester Cough Questionnaire in non-cystic fibrosis bronchiectasis. Chron Respir Dis. 2016 May;13:128–36.

252. Pollock J, Polverino E, Dhar R, Dimakou K, Traversi L, Bossios A, et al. Use of inhaled corticosteroids in bronchiectasis: data from the European Bronchiectasis Registry (EMBARC). Thorax [Internet]. 2025 Mar 23;thorax-2024-221825. Available from: https://thorax.bmj.com/lookup/doi/10.1136/thorax-2024-221825

253. Martínez-García MÁ, Máiz L, Olveira C, Girón RM, de la Rosa D, Blanco M, et al. Spanish Guidelines on the Evaluation and Diagnosis of Bronchiectasis in Adults. Arch Bronconeumol (English Ed [Internet]. 2018 Feb 1 [cited 2021 Jun 4];54(2):79–87. Available from: https://www.archbronconeumol.org/en-spanish-guidelines-on-evaluation-diagnosis-articulo-S157921291730383X

254. Li K, Liu L, Ou Y. The efficacy of azithromycin to prevent exacerbation of non-cystic fibrosis bronchiectasis: a meta-analysis of randomized controlled studies. J Cardiothorac Surg [Internet]. 2022 Oct 11;17(1):266. Available from:

https://cardiothoracicsurgery.biomedcentral.com/articles/10.1186/s13019-022-01882-y

255. Amati F, Gramegna A, Contarini M, Tarsia P, Bellofiore A, Blasi F, et al. Site of care and multidisciplinary approach. In: Bronchiectasis [Internet]. European Respiratory Society; 2018. Available from: http://publications.ersnet.org/lookup/doi/10.1183/2312508X.10017117

256. Chalmers JD, Mall MA, McShane PJ, Nielsen KG, Shteinberg M, Sullivan SD, et al. A systematic literature review of the clinical and socioeconomic burden of bronchiectasis. Eur Respir Rev [Internet]. 2024 Jul 4;33(173):240049. Available from: https://publications.ersnet.org/lookup/doi/10.1183/16000617.0049-2024

257. Eden E, Choate R, Barker A, Addrizzo-Harris D, Aksamit TR, Daley CL, et al. The Clinical Features of Bronchiectasis Associated with Alpha-1 Antitrypsin Deficiency, Common Variable Immunodeficiency and Primary Ciliary Dyskinesia--Results from the U.S. Bronchiectasis Research Registry. Chronic Obstr Pulm Dis J COPD Found [Internet]. 2019;6(2):145–53. Available from: https://journal.copdfoundation.org/jcopdf/id/1229/The-Clinical-Features-of-Bronchiectasis-Associated-with-Alpha-1-Antitrypsin-Deficiency-Common-Variable-Immunodeficiency-and-Primary-Ciliary-Dyskinesia-Results-from-the-US-Bronchiectasis-Research-Registry

258. Shen H, Hua W, Wang P, Li W. A new phenotype of asthma: chest tightness as the sole presenting manifestation. Ann Allergy, Asthma Immunol [Internet]. 2013 Sep;111(3):226–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1081120613004353

259. Zhong N. Chest tightness variant asthma: deja vu all over again. J Thorac Dis [Internet]. 2014 May;6(5):407–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24822094

260. Eurostat. Tobacco consumption statistics [Internet]. 2022. Available from: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Tobacco_consumption_statistics

261. Yang B, Han K, Kim B, Kang HK, Kim JS, Kim E-G, et al. Association between Smoking Status and Incident Non-Cystic Fibrosis Bronchiectasis in Young Adults: A Nationwide Population-Based Study. J Pers Med [Internet]. 2022 Apr 26;12(5):691. Available from: https://www.mdpi.com/2075-4426/12/5/691

262. Shteinberg M, Nassrallah N, Jrbashyan J, Uri N, Stein N, Adir Y. Upper airway involvement in bronchiectasis is marked by early onset and allergic features. ERJ Open Res. 2018;

263. Guilemany JM, Angrill J, Alobid I, Centellas S, Pujols L, Bartra J, et al. United airways again: high prevalence of rhinosinusitis and nasal polyps in bronchiectasis. Allergy. 2009 May;64(5):790–7.

264. NİKSARLIOĞLU EY, Niksarlioğlu EY, Işik R, Uysal MA, Ünal D, Çamsari G. Prevalence of atopy and allergic rhinitis in patients with adult non-cystic fibrosis bronchiectasis. TURKISH J Med Sci [Internet]. 2019 Apr 18;49(2):551–7. Available from: https://journals.tubitak.gov.tr/medical/vol49/iss2/16

265. Sundaresan AS, Hirsch AG, Young AJ, Pollak J, Tan BK, Schleimer RP, et al. Longitudinal Evaluation of Chronic Rhinosinusitis Symptoms in a Population-Based Sample. J Allergy Clin Immunol Pract [Internet]. 2018 Jul;6(4):1327-1335.e3. Available from: https://linkinghub.elsevier.com/retrieve/pii/S221321981730795X

266. Huerta A, Donaldson GC, Singh R, Mackay AJ, Allinson JP, Brill SE, et al. Upper Respiratory

Symptoms Worsen over Time and Relate to Clinical Phenotype in Chronic Obstructive Pulmonary Disease. Ann Am Thorac Soc [Internet]. 2015 Jul;12(7):997–1004. Available from: https://www.atsjournals.org/doi/10.1513/AnnalsATS.201408-359OC

267. WILSON CB, JONES PW, O'LEARY CJ, COLE PJ, WILSON R. Validation of the St. George's Respiratory Questionnaire in Bronchiectasis. Am J Respir Crit Care Med [Internet]. 1997 Aug 1;156(2):536–41. Available from: https://www.atsjournals.org/doi/10.1164/ajrccm.156.2.9607083

268. Sami R, Zohal M, Khanali F, Esmailzadehha N. Quality of life and its determinants in patients with noncystic fibrosis bronchiectasis. J Res Med Sci [Internet]. 2021 Jan;26(1):27. Available from: https://journals.lww.com/10.4103/jrms.JRMS_665_20

269. Martínez-García MA, Perpiñá-Tordera M, Román-Sánchez P, Soler-Cataluña JJ. Quality-of-life determinants in patients with clinically stable bronchiectasis. Chest. 2005;

270. Lanza FC, Castro RAS, de Camargo AA, Zanatta DJM, Rached S, Athanazio R, et al. COPD Assessment Test (CAT) is a Valid and Simple Tool to Measure the Impact of Bronchiectasis on Affected Patients. COPD J Chronic Obstr Pulm Dis [Internet]. 2018 Sep 3;15(5):512–9. Available from: https://www.tandfonline.com/doi/full/10.1080/15412555.2018.1540034

271. Finch S, Laska IF, Abo-Leyah H, Fardon TC, Chalmers JD. Validation of the COPD Assessment Test (CAT) as an Outcome Measure in Bronchiectasis. Chest [Internet]. 2020 Apr 1 [cited 2021 Mar 9];157(4):815–23. Available from: https://pubmed.ncbi.nlm.nih.gov/31730832/

272. McLeese RH, Spinou A, Alfahl Z, Tsagris M, Elborn JS, Chalmers JD, et al. Psychometrics of health-related quality of life questionnaires in bronchiectasis: a systematic review and meta-analysis. Eur Respir J [Internet]. 2021 Nov;58(5):2100025. Available from: https://publications.ersnet.org/lookup/doi/10.1183/13993003.00025-2021

273. Tomaszewski EL, Atkinson MJ, Janson C, Karlsson N, Make B, Price D, et al. Chronic Airways Assessment Test: psychometric properties in patients with asthma and/or COPD. Respir Res [Internet]. 2023 Apr 8;24(1):106. Available from: https://respiratory-research.biomedcentral.com/articles/10.1186/s12931-023-02394-6

274. Lee AL, Nicolson CHH, Bondarenko J, Button BM, Ellis S, Stirling RG, et al. The clinical impact of self-reported symptoms of chronic rhinosinusitis in people with bronchiectasis. Immunity, Inflamm Dis. 2022 Jan;10:101–10.

275. Piñeros-García LM, González-Sánchez NI, Calvo-Henriquez C, Jesús Rojas-Lechuga M, Hopkins C, Mullol J, et al. SNOT-22 in general population, a Spanish cohort study with an updated meta-analysis. Available from: https://doi.org/10.4193/Rhin24.033

276. Thomas ET, Guppy M, Straus SE, Bell KJL, Glasziou P. Rate of normal lung function decline in ageing adults: a systematic review of prospective cohort studies. BMJ Open [Internet]. 2019 Jun 27;9(6):e028150. Available from: https://bmjopen.bmj.com/lookup/doi/10.1136/bmjopen-2018-028150

277. Borekci S, Gundogdu S, Harbiyeli DO, Musellim B. Annual FEV1 Loss in Patients with Noncystic Fibrosis Bronchiectasis and Affecting Factors. South Med J [Internet]. 2022 May;115(5):328–32. Available from: http://sma.org/southern-medical-journal/article/annual-fev1-loss-in-patients-with-

noncystic-fibrosis-bronchiectasis-and-affecting-factors

278. Sperlich JM, Grimbacher B, Soetedjo V, Workman S, Burns SO, Lowe DM, et al. Predictive Factors for and Complications of Bronchiectasis in Common Variable Immunodeficiency Disorders. J Clin Immunol. 2022 Apr;42:572–81.

279. Marthin JK, Petersen N, Skovgaard LT, Nielsen KG. Lung Function in Patients with Primary Ciliary Dyskinesia. Am J Respir Crit Care Med [Internet]. 2010 Jun 1;181(11):1262–8. Available from: https://www.atsjournals.org/doi/10.1164/rccm.200811-1731OC

280. Zhang K, Kant A, Boon M, Borrelli M, Constant C, Castillo Corullon S, et al. Natural variability of lung function in primary ciliary dyskinesia: longitudinal analysis from the PROVALF-PCD cohort. ERJ Open Res [Internet]. 2025 Mar 28;01115–2024. Available from: https://publications.ersnet.org/lookup/doi/10.1183/23120541.01115-2024

281. Martinez-Garcia MA, Athanazio RA, Girón R, Máiz-Carro L, de la Rosa D, Olveira C, de Gracia J, Vendrell M, Prados-Sánchez C, Gramblicka G, Corso Pereira M, Lundgren FL, Fernandes De Figueiredo M, Arancibia F RS. Predicting high risk of exacerbations in bronchiectasis: the E-FACED score. Int J Chron Obs Pulmon Dis. 2017;18(12):275:284.

282. Dimakou K, Triantafillidou C, Toumbis M, Tsikritsaki K, Malagari K, Bakakos P. Non CF-bronchiectasis: Aetiologic approach, clinical, radiological, microbiological and functional profile in 277 patients. Respir Med [Internet]. 2016;116:1–7. Available from: http://dx.doi.org/10.1016/j.rmed.2016.05.001

283. Martinez-García MA, Oscullo G, Posadas T, Zaldivar E, Villa C, Dobarganes Y, et al. Pseudomonas aeruginosa and lung function decline in patients with bronchiectasis. Clin Microbiol Infect [Internet]. 2021 Mar;27(3):428–34. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1198743X20302123

284. Guan W, Gao Y, Xu G, Lin Z, Tang Y, Li H, et al. Characterization of Lung Function Impairment in Adults with Bronchiectasis. Ji H-L (James), editor. PLoS One [Internet]. 2014 Nov 18;9(11):e113373. Available from: https://dx.plos.org/10.1371/journal.pone.0113373

285. Mariani AW, Vallilo CC, De Albuquerque ALP, Salge JM, Augusto MC, Suesada MM, et al. Preoperative evaluation for lung resection in patients with bronchiectasis: should we rely on standard lung function evaluation? Eur J Cardiothorac Surg [Internet]. 2021 Jun 1 [cited 2025 Apr 18];59(6):1272–8. Available from: https://pubmed.ncbi.nlm.nih.gov/33491053/

286. de Jong PA. Progression of lung disease on computed tomography and pulmonary function tests in children and adults with cystic fibrosis. Thorax [Internet]. 2005 Oct 21;61(1):80–5. Available from: https://thorax.bmj.com/lookup/doi/10.1136/thx.2005.045146

287. Loebinger MR, Wells AU, Hansell DM, Chinyanganya N, Devaraj A, Meister M, et al. Mortality in bronchiectasis: A long-term study assessing the factors influencing survival. Eur Respir J. 2009;

288. Roberts HR, Wells AU, Rubens MB, Cole PJ, Hansell DM, Milne DG, et al. Airflow obstruction in bronchiectasis: correlation between computed tomography features and pulmonary function tests. Thorax [Internet]. 2000 Mar 1 [cited 2025 Apr 18];55(3):198–204. Available from:

https://thorax.bmj.com/content/55/3/198

289. Thurlbeck W, AM C. Chronic airflow obstruction. In: Thurlbeck, Churg, editors. Pathology of the lung.). New Yor. New York, NY: Thieme Medical Publishers Inc; 1995. p. 739–825.

290. Konstantinos Katsoulis K, Kostikas K, Kontakiotis T. Techniques for assessing small airways function: Possible applications in asthma and COPD. Respir Med [Internet]. 2016 Oct;119:e2–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0954611113001753

291. Turato G, Zuin R, Miniati M, Baraldo S, Rea F, Beghé B, et al. Airway Inflammation in Severe Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med [Internet]. 2002 Jul 1;166(1):105–10. Available from: https://www.atsjournals.org/doi/10.1164/rccm.2111084

292. Kanj AN, Samhouri BF, Poliszuk D, Lim KG, Hoskote SS. Isolated Elevation in Lung Residual Volume Is Associated With Airway Diseases. Respir Care [Internet]. 2022 Jul 1;67(7):842–9. Available from: https://www.liebertpub.com/doi/10.4187/respcare.09687

293. Whitwell F. A Study of the Pathology and Pathogenesis of Bronchiectasis. Thorax [Internet]. 1952 Sep 1;7(3):213–39. Available from: https://thorax.bmj.com/lookup/doi/10.1136/thx.7.3.213

294. Dickinson JD, Evans CM, Dickey BF. Small Airways in Non–Cystic Fibrosis Bronchiectasis. Am J Respir Crit Care Med [Internet]. 2024 Feb 15;209(4):347–9. Available from: https://www.atsjournals.org/doi/10.1164/rccm.202312-2275ED

295. Asakura T, Okuda K, Chen G, Dang H, Kato T, Mikami Y, et al. Proximal and Distal Bronchioles Contribute to the Pathogenesis of Non–Cystic Fibrosis Bronchiectasis. Am J Respir Crit Care Med [Internet]. 2024 Feb 15;209(4):374–89. Available from: https://www.atsjournals.org/doi/10.1164/rccm.202306-1093OC

296. Mikami Y, Grubb BR, Rogers TD, Dang H, Asakura T, Kota P, et al. Chronic airway epithelial hypoxia exacerbates injury in muco-obstructive lung disease through mucus hyperconcentration. Sci Transl Med [Internet]. 2023 Jun 7;15(699). Available from: https://www.science.org/doi/10.1126/scitranslmed.abo7728

297. Lopes AJ, Camilo GB, de Menezes SLS, Guimaraes FS. Impact of Different Etiologies of Bronchiectasis on the Pulmonary Function Tests. Clin Med Res [Internet]. 2015 Mar 1;13(1):12–9. Available from: http://www.clinmedres.org/cgi/doi/10.3121/cmr.2014.1236

298. Zhang K, Zou X, Ma Z, Liu X, Qiu C, Xie L, et al. Risk Factors Associated with Impairment in Pulmonary Diffusing Capacity among Patients with Noncystic Fibrosis Bronchiectasis. Santus P, editor. Can Respir J [Internet]. 2022 Mar 9;2022:1–10. Available from: https://www.hindawi.com/journals/crj/2022/8175508/

299. King PT, Holdsworth SR, Freezer NJ, Villanueva E, Farmer MW, Guy P, et al. Lung diffusing capacity in adult bronchiectasis: a longitudinal study. Respir Care [Internet]. 2010 Dec;55(12):1686–92. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21122177

300. Öcal S, Portakal O, Öcal A, Demir AU, Topeli A, Çöplü L. Factors associated with pulmonary hypertension and long-term survival in bronchiectasis subjects. Respir Med [Internet]. 2016 Oct;119:109–14. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0954611116302220

301. Alzeer A. HRCT score in bronchiectasis: Correlation with pulmonary function tests and pulmonary artery pressure. Ann Thorac Med [Internet]. 2008;3(3):82. Available from: https://journals.lww.com/10.4103/1817-1737.39675

302. Ellis DA, Thornley PE, Wightman AJ, Walker M, Chalmers J, Crofton JW. Present outlook in bronchiectasis: clinical and social study and review of factors influencing prognosis. Thorax [Internet]. 1981 Sep 1;36(9):659–64. Available from: https://thorax.bmj.com/lookup/doi/10.1136/thx.36.9.659

303. Alzeer AH, Al-Mobeirek AF, Al-Otair HAK, Elzamzamy UAF, Joherjy IA, Shaffi AS. Right and Left Ventricular Function and Pulmonary Artery Pressure in Patients With Bronchiectasis. Chest [Internet]. 2008 Feb;133(2):468–73. Available from: https://linkinghub.elsevier.com/retrieve/pii/S001236921549097X

304. van der Lee I, Zanen P, van den Bosch JMM, Lammers J-WJ. Pattern of diffusion disturbance related to clinical diagnosis: The KCO has no diagnostic value next to the DLCO. Respir Med [Internet]. 2006 Jan;100(1):101–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0954611105001794

305. Goldin J, Cascella M. Diffusing Capacity of the Lungs for Carbon Monoxide [Internet]. StatPearls. 2025. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27566377

306. Jeong HJ, Lee H, Carriere KC, Kim JH, Han J-H, Shin B, et al. Effects of long-term bronchodilators in bronchiectasis patients with airflow limitation based on bronchodilator response at baseline. Int J Chron Obstruct Pulmon Dis [Internet]. 2016 Nov;Volume 11:2757–64. Available from: https://www.dovepress.com/effects-of-long-term-bronchodilators-in-bronchiectasis-patients-with-a-peer-reviewed-article-COPD

307. Guan WJ, Gao YH, Xu G, Li HM, Yuan JJ, Zheng JP, et al. Bronchodilator response in adults with bronchiectasis: correlation with clinical parameters and prognostic implications. J Thorac Dis [Internet]. 2016 [cited 2025 Apr 18];8(1):14–23. Available from: https://jtd.amegroups.org/article/view/6471/html

308. Sokol G, Vilozni D, Hakimi R, Lavie M, Sarouk I, Bar B El, et al. The Short-Term Effect of Breathing Tasks Via an Incentive Spirometer on Lung Function Compared With Autogenic Drainage in Subjects With Cystic Fibrosis. Respir Care [Internet]. 2015 Dec 1 [cited 2025 Apr 18];60(12):1819–25. Available from: https://pubmed.ncbi.nlm.nih.gov/26374905/

309. Shoemark A, Shteinberg M, De Soyza A, Haworth CS, Richardson H, Gao Y, et al. Characterization of Eosinophilic Bronchiectasis: A European Multicohort Study. Am J Respir Crit Care Med [Internet]. 2022 Apr 15;205(8):894–902. Available from: https://www.atsjournals.org/doi/10.1164/rccm.202108-1889OC

310. Oriano M, Gramegna A, Amati F, D'Adda A, Gaffuri M, Contoli M, et al. T2-High Endotype and Response to Biological Treatments in Patients with Bronchiectasis. Biomedicines [Internet]. 2021 Jul 2 [cited 2021 Dec 24];9(7):772. Available from: https://pubmed.ncbi.nlm.nih.gov/34356836/

311. Martínez-García MÁ, Méndez R, Olveira C, Girón R, García-Clemente M, Máiz L, et al. The U-Shaped Relationship Between Eosinophil Count and Bronchiectasis Severity. Chest [Internet]. 2023 Sep;164(3):606–13. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0012369223006049

312. Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. Lancet Respir Med [Internet]. 2015 Jun;3(6):435–42. Available from: https://linkinghub.elsevier.com/retrieve/pii/S221326001500106X

313. Aliberti S, Sotgiu G, Blasi F, Saderi L, Posadas T, Martinez Garcia MA. Blood eosinophils predict inhaled fluticasone response in bronchiectasis. Eur Respir J [Internet]. 2020 Aug;56(2):2000453. Available from: https://publications.ersnet.org/lookup/doi/10.1183/13993003.00453-2020

314. Shoemark A, Devaraj A, Meister M, Ozerovitch L, Hansell DM, Wilson R. Elevated peripheral airway nitric oxide in bronchiectasis reflects disease severity. Respir Med [Internet]. 2011 Jun [cited 2025 Jun 3];105(6):885–91. Available from: https://pubmed.ncbi.nlm.nih.gov/21398103/

315. Cho Y-J, Lim H-J, Park JS, Lee JH, Lee C-T, Yoon H Il. Measurement of Fractional Exhaled Nitric Oxide in Stable Bronchiectasis. Tuberc Respir Dis (Seoul) [Internet]. 2013 Jan [cited 2025 Jun 3];74(1):7. Available from: https://pubmed.ncbi.nlm.nih.gov/23390447/

316. Malli F, Gouvani A, Dimeas I, Ladias S, Papathanasiou I V., Gourgoulianis KI, et al. Exhaled Nitric Oxide (FeNO) in Patients Hospitalized for an Exacerbation of Bronchiectasis and/or COPD: FeNO Levels in COPD and Bronchiectasis. Adv Exp Med Biol [Internet]. 2021 [cited 2025 Jun 3];1337:323–30. Available from: https://pubmed.ncbi.nlm.nih.gov/34972920/

317. Tsang KW, Tan KC, Ho PL, Ooi GC, Khong PL, Leung R, et al. Exhaled nitric oxide in bronchiectasis: the effects of inhaled corticosteroid therapy. Int J Tuberc Lung Dis [Internet]. 2004 Nov;8(11):1301–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15581196

318. Traiyan S, Manuyakorn W, Kanchongkittiphon W, Sasisakulporn C, Jotikasthira W, Kiewngam P, et al. Skin Prick Test Versus Phadiatop as a Tool for Diagnosis of Allergic Rhinitis in Children. Am J Rhinol Allergy [Internet]. 2021 Jan 27;35(1):98–106. Available from: https://journals.sagepub.com/doi/10.1177/1945892420938300

319. Zhang P-A, Wang J-L, Fu S-Y, Luo H-L, Qin R-D, Li J. Mediators of the association between allergic diseases and bronchiectasis: A bi-directional univariable and multivariable Mendelian randomization study and mediation analysis. World Allergy Organ J [Internet]. 2025 Mar;18(3):101038. Available from: http://www.ncbi.nlm.nih.gov/pubmed/40151543

320. Chen YF, Hou HH, Chien N, Lu KZ, Chen YY, Hung ZC, et al. Type 2 Biomarkers and Their Clinical Implications in Bronchiectasis: A Prospective Cohort Study. Lung [Internet]. 2024 Oct 1 [cited 2025 Jun 3];202(5). Available from: https://pubmed.ncbi.nlm.nih.gov/38884647/

321. Vidaillac C, Chotirmall SH. Pseudomonas aeruginosa in bronchiectasis: infection, inflammation, and therapies. Expert Rev Respir Med [Internet]. 2021 May 4;15(5):649–62. Available from: https://www.tandfonline.com/doi/full/10.1080/17476348.2021.1906225

322. Posadas T, Oscullo G, Zaldivar E, Villa C, Dobarganes Y, Girón R, et al. C-Reactive Protein Concentration in Steady-State Bronchiectasis: Prognostic Value of Future Severe Exacerbations. Data From the Spanish Registry of Bronchiectasis (RIBRON). Arch Bronconeumol [Internet]. 2021 Jan;57(1):21–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0300289619306258

323. Chalmers JD, Hill AT. Mechanisms of immune dysfunction and bacterial persistence in non-cystic fibrosis bronchiectasis. Mol Immunol. 2013 Aug;55(1):27–34.

324. Choate R, Aksamit TR, Mannino D, Addrizzo-Harris D, Barker A, Basavaraj A, et al. Pseudomonas aeruginosa associated with severity of non-cystic fibrosis bronchiectasis measured by the modified bronchiectasis severity score (BSI) and the FACED: The US bronchiectasis and NTM Research Registry (BRR) study. Respir Med [Internet]. 2021 Feb;177:106285. Available from: https://linkinghub.elsevier.com/retrieve/pii/S095461112030425X

325. McDonnell MJ, Aliberti S, Goeminne PC, Dimakou K, Zucchetti SC, Davidson J, et al. Multidimensional severity assessment in bronchiectasis: an analysis of seven European cohorts. Thorax. 2016 Dec;71(12):1110–8.

326. Solarat B, Perea L, Faner R, de La Rosa D, Martínez-García MÁ, Sibila O. Pathophysiology of Chronic Bronchial Infection in Bronchiectasis. Arch Bronconeumol [Internet]. 2023 Feb;59(2):101–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0300289622005257

327. Chotirmall SH. The emergence of i Aspergillus i species in chronic respiratory disease. Front Biosci [Internet]. 2017;9(1):477. Available from: https://imrpress.com/journal/FBS/9/1/10.2741/S477

328. Blomquist A, Inghammar M, Al Shakirchi M, Ericson P, Krantz C, Svedberg M, et al. Persistent Aspergillus fumigatus infection in cystic fibrosis: impact on lung function and role of treatment of asymptomatic colonization—a registry-based case–control study. BMC Pulm Med [Internet]. 2022 Dec 5;22(1):263. Available from: https://bmcpulmmed.biomedcentral.com/articles/10.1186/s12890-022-02054-3

329. Choi H, Chalmers JD. Bronchiectasis exacerbation: a narrative review of causes, risk factors, management and prevention. Ann Transl Med [Internet]. 2023 Jan;11(1):25–25. Available from: https://atm.amegroups.com/article/view/104705/html

330. Finch S, McDonnell MJ, Abo-Leyah H, Aliberti S, Chalmers JD. A Comprehensive Analysis of the Impact of Pseudomonas aeruginosa Colonization on Prognosis in Adult Bronchiectasis. Ann Am Thorac Soc [Internet]. 2015 Nov 1 [cited 2021 Nov 25];12(11):1602–11. Available from: https://pubmed.ncbi.nlm.nih.gov/26356317/

331. Bedi P, Chalmers JD, Goeminne PC, Mai C, Saravanamuthu P, Velu PP, et al. The BRICS (Bronchiectasis Radiologically Indexed CT Score): A Multicenter Study Score for Use in Idiopathic and Postinfective Bronchiectasis. Chest. 2018;153(5).

332. Singh A, Bhalla AS, Jana M. Bronchiectasis Revisited: Imaging-Based Pattern Approach to Diagnosis. Curr Probl Diagn Radiol [Internet]. 2019 Jan 1 [cited 2021 Mar 17];48(1):53–60. Available from: https://pubmed.ncbi.nlm.nih.gov/29530453/

333. Bueno J, Flors L. The role of imaging in the diagnosis of bronchiectasis: the key is in the distribution. Radiologia. 2018 Jan 1;60(1):85–9.

334. Singh A, Bhalla AS, Jana M. Bronchiectasis Revisited: Imaging-Based Pattern Approach to Diagnosis. Curr Probl Diagn Radiol [Internet]. 2019 Jan 1 [cited 2025 Apr 24];48(1):53–60. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0363018817302670

335. Loubeyre P, Paret M, Revel D, Wiesendanger T, Brune J. Thin-Section CT Detection of Emphysema Associated With Bronchiectasis and Correlation With Pulmonary Function Tests. Chest [Internet]. 1996 Feb;109(2):360–5. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0012369215456600

336. Tang X, Bi J, Yang D, Chen S, Li Z, Chen C, et al. Emphysema is an independent risk factor for 5-year mortality in patients with bronchiectasis. Clin Respir J [Internet]. 2017 Nov 11;11(6):887–94. Available from: https://onlinelibrary.wiley.com/doi/10.1111/crj.12432

337. Bedi P, Chalmers JD, Goeminne PC, Mai C, Saravanamuthu P, Velu PP, et al. The BRICS (Bronchiectasis Radiologically Indexed CT Score): A Multicenter Study Score for Use in Idiopathic and Postinfective Bronchiectasis. Chest. 2018 May;153:1177–86.

338. Chua F, Laurent GJ. Neutrophil elastase: Mediator of extracellular matrix destruction and accumulation. In: Proceedings of the American Thoracic Society. 2006. p. 424–7.

339. Pieters ALP, van der Veer T, Meerburg JJ, Andrinopoulou ER, van der Eerden MM, Ciet P, et al. Structural Lung Disease and Clinical Phenotype in Bronchiectasis Patients: The EMBARC CT Study. Am J Respir Crit Care Med [Internet]. 2024 Jul 1 [cited 2025 Apr 24];210(1):87–96. Available from: https://www.atsjournals.org/doi/pdf/10.1164/rccm.202311-2109OC?download=true

340. Fan Y, Li Z, Jiang N, Zhou Y, Song J, Yu F, et al. Prediction of Clinical Bronchiectasis from Asymptomatic Radiological Bronchiectasis. J Inflamm Res [Internet]. 2025 Apr [cited 2025 Apr 24];18:4995–5009. Available from: https://pubmed.ncbi.nlm.nih.gov/40248591/

341. Chan R, Duraikannu C, Lipworth B. Clinical Associations of Mucus Plugging in Moderate to Severe Asthma. J Allergy Clin Immunol Pract [Internet]. 2023 Jan;11(1):195-199.e2. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2213219822009436

342. Krings JG, Gierada DS. Do Biologic Therapies Decrease Mucus Plugging in Asthma? NEJM Evid [Internet]. 2023 Sep 26;2(10). Available from: https://evidence.nejm.org/doi/10.1056/EVIDe2300179

343. Svenningsen S, Kjarsgaard M, Haider E, Venegas C, Konyer N, Friedlander Y, et al. Effects of Dupilumab on Mucus Plugging and Ventilation Defects in Patients with Moderate-to-Severe Asthma: A Randomized, Double-Blind, Placebo-Controlled Trial. Am J Respir Crit Care Med [Internet]. 2023 Nov 1;208(9):995–7. Available from: https://www.atsjournals.org/doi/10.1164/rccm.202306-1102LE

344. Ren J, Chen A, Wang J, Chang C, Wang J, Sun L, et al. Association of blood total immunoglobulin E and eosinophils with radiological features of bronchiectasis. BMC Pulm Med [Internet]. 2023 Aug 31;23(1):316. Available from: https://bmcpulmmed.biomedcentral.com/articles/10.1186/s12890-023-02607-0

345. Lynch DA, Newell JD, Tschomper BA, Cink TM, Newman LS, Bethel R. Uncomplicated asthma in adults: comparison of CT appearance of the lungs in asthmatic and healthy subjects. Radiology [Internet]. 1993 Sep;188(3):829–33. Available from: http://pubs.rsna.org/doi/10.1148/radiology.188.3.8351357

346. Nie Z, Vonder M, de Vries M, Yang X, Oudkerk M, Slebos DJ, et al. Co-occurrence of bronchiectasis, airway wall thickening, and emphysema in Chinese low-dose CT screening. Eur Radiol. 2025;

347. Juliusson G, Gudmundsson G. Diagnostic imaging in adult non-cystic fibrosis bronchiectasis. Breathe [Internet]. 2019 Sep;15(3):190–7. Available from: http://publications.ersnet.org/lookup/doi/10.1183/20734735.0009-2019

348. Ooi GC, Khong PL, Chan-Yeung M, Ho JCM, Chan PKS, Lee JCK, et al. High-resolution CT quantification of bronchiectasis: Clinical and functional correlation. Radiology. 2002;225:663–72.

349. Tan WC, Hague CJ, Leipsic J, Bourbeau J, Zheng L, Li PZ, et al. Findings on thoracic computed tomography scans and respiratory outcomes in persons with and without chronic obstructive pulmonary disease: A population-based cohort study. PLoS One. 2016 Nov;11.

350. Yamamoto Y, Kuge T, Miki K, Tsujino K, Kawasaki T, Matsuki T, et al. Impact of bronchial wall thickness on airflow obstruction in bronchiectasis. Respir Physiol Neurobiol. 2022 Jan;295.

351. Pieters ALP, Lv Q, Meerburg JJ, van der Veer T, Andrinopoulou E-R, Ciet P, et al. Automated method of bronchus and artery dimension measurement in an adult bronchiectasis population. ERJ Open Res [Internet]. 2024 Nov;10(6):00231–2024. Available from: https://publications.ersnet.org/lookup/doi/10.1183/23120541.00231-2024

352. Perez-Rovira A, Kuo W, Petersen J, Tiddens HAWM, De Bruijne M. Automatic airway-artery analysis on lung CT to quantify airway wall thickening and bronchiectasis. Med Phys. 2016 Oct;43:5736–44.

353. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner Society: Glossary of Terms for Thoracic Imaging. Radiology [Internet]. 2008 Mar;246(3):697–722. Available from: http://pubs.rsna.org/doi/10.1148/radiol.2462070712

354. El-Sherief AH, Gilman MD, Healey TT, Tambouret RH, Shepard J-AO, Abbott GF, et al. Clear Vision Through the Haze: A Practical Approach to Ground-Glass Opacity. Curr Probl Diagn Radiol [Internet]. 2014 May;43(3):140–58. Available from: https://linkinghub.elsevier.com/retrieve/pii/S036301881400005X

355. Dettmer S, Ringshausen FC, Fuge J, Maske HL, Welte T, Wacker F, et al. Computed Tomography in Adults with Bronchiectasis and Nontuberculous Mycobacterial Pulmonary Disease: Typical Imaging Findings. J Clin Med [Internet]. 2021 Jun 21;10(12):2736. Available from: https://www.mdpi.com/2077-0383/10/12/2736

356. Dettmer S, Ringshausen F, Vogel-Claussen J, Fuge J, Faschkami A, Shin H oh, et al. Computed tomography in adult patients with primary ciliary dyskinesia: Typical imaging findings. 2018 Feb 1 [cited 2021 Nov 24];13(2). Available from: https://pubmed.ncbi.nlm.nih.gov/29408869/

357. Lynch DA, Austin JHM, Hogg JC, Grenier PA, Kauczor HU, Bankier AA, et al. CT-definable subtypes of chronic obstructive pulmonary disease: A statement of the fleischner society1. Radiology. 2015 Oct;277:192–205.

358. Nishino M, Siewert B, Roberts DH, Gautam S, Boiselle PM, Raptopoulos V, et al. Excessive Collapsibility of Bronchi in Bronchiectasis. J Comput Assist Tomogr [Internet]. 2006 May;30(3):474–8. Available from: http://journals.lww.com/00004728-200605000-00020

359. Miller WT, Chatzkel J, Hewitt MG. Expiratory Air Trapping on Thoracic Computed Tomography. A Diagnostic Subclassification. Ann Am Thorac Soc [Internet]. 2014 Jul;11(6):874–81. Available from:

https://www.atsjournals.org/doi/10.1513/AnnalsATS.201311-390OC

360. Bak SH, Kim S, Hong Y, Heo J, Lim M-N, Kim WJ. Quantitative computed tomography features and clinical manifestations associated with the extent of bronchiectasis in patients with moderate-to-severe COPD. Int J Chron Obstruct Pulmon Dis [Internet]. 2018 May;Volume 13:1421–31. Available from: https://www.dovepress.com/quantitative-computed-tomography-features-and-clinical-manifestations--peer-reviewed-article-COPD

361. Bugenhagen SM, Grant JCE, Rosenbluth DB, Bhalla S. Update on the Role of Chest Imaging in Cystic Fibrosis. Vol. 44, Radiographics : a review publication of the Radiological Society of North America, Inc. 2024. p. e240008.

362. Robinson TE, Goris ML, Moss RB, Tian L, Kan P, Yilma M, et al. Mucus plugging, air trapping, and bronchiectasis are important outcome measures in assessing progressive childhood cystic fibrosis lung disease. Pediatr Pulmonol. 2020 Apr 1;55(4):929–38.

363. DeBoer EM, Swiercz W, Heltshe SL, Anthony MM, Szefler P, Klein R, et al. Automated ct scan scores of bronchiectasis and air trapping in cystic fibrosis. Chest [Internet]. 2014 [cited 2025 Apr 24];145(3):593–603. Available from: https://pubmed.ncbi.nlm.nih.gov/24114359/

364. Grenier PA, Brun AL, Longchampt E, Lipski M, Mellot F, Catherinot E. Primary immunodeficiency diseases of adults: a review of pulmonary complication imaging findings. Vol. 34, European Radiology. Springer Science and Business Media Deutschland GmbH; 2024. p. 4142–54.

365. Ramzi N, Jamee M, Bakhtiyari M, Rafiemanesh H, Zainaldain H, Tavakol M, et al. Bronchiectasis in common variable immunodeficiency: A systematic review and meta-analysis. Vol. 55, Pediatric Pulmonology. John Wiley and Sons Inc.; 2020. p. 292–9.

366. Spinou A, Almagro M, Harris B, Boyd J, Berg T, Herrero-Cortina B, et al. Diagnostic delay and access to care in bronchiectasis: data from the EMBARC/ELF patient survey. Eur Respir J [Internet]. 2024 Jul;64(1). Available from: http://www.ncbi.nlm.nih.gov/pubmed/38843909

367. Livnat G, Yoseph RB, Nir V, Hakim F, Yigla M, Bentur L. Evaluation of High-Sensitivity Serum CRP Levels Compared to Markers of Airway Inflammation and Allergy as Predictors of Methacholine Bronchial Hyper-Responsiveness in Children. Lung [Internet]. 2015 Feb 21;193(1):39–45. Available from: http://link.springer.com/10.1007/s00408-014-9658-6

368. Hunninghake JC, McCullough SB, Aden JK, Hayes JA, McCann ET, Morris MJ. Baseline Spirometry as a Predictor of Positive Methacholine Challenge Testing for Exertional Dyspnea. Respir Care [Internet]. 2022 Jun;67(6):694–701. Available from: http://www.ncbi.nlm.nih.gov/pubmed/35042746

369. Reinsberg M, Siebert S, Dreher C, Bogs T, Ganschow R, Yavuz ST. Predictors of Airway Hyperresponsiveness in Symptomatic Children with Normal Spirometry and Suspicious of Possible Asthma. Int Arch Allergy Immunol [Internet]. 2022;183(5):517–25. Available from: http://www.ncbi.nlm.nih.gov/pubmed/34903689

370. Shin S, Whitmore GA, Boulet L-P, Boulay M-È, Côté A, Bergeron C, et al. Anticipating undiagnosed asthma in symptomatic adults with normal pre- and post-bronchodilator spirometry: a decision tool for bronchial challenge testing. BMC Pulm Med [Internet]. 2023 Dec 9;23(1):496. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/38071285

371. Ip M, Lam WK, So SY, Liong E, Chan CY, Tse KM. Analysis of factors associated with bronchial hyperreactivity to methacholine in bronchiectasis. Lung [Internet]. 1991;169(1):43–51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2011043

372. Pang J, Chan HS, Sung JY. Prevalence of asthma, atopy, and bronchial hyperreactivity in bronchiectasis: a controlled study. Thorax [Internet]. 1989 Nov;44(11):948–51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2595637

373. Guilemany JM, Angrill J, Alobid I, Centellas S, Prades E, Roca J, et al. United airways: The impact of chronic rhinosinusitis and nasal polyps in bronchiectasic patient's quality of life. Allergy Eur J Allergy Clin Immunol. 2009 Sep;64:1524–9.