Airway Inflammation and Remodeling in Focus

Clinical and radiological studies in bronchiectasis, asthma and COPD

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Luchtwegontsteking en Remodellering in Beeld

Klinische en radiologische studies van bronchiëctasieën, astma en COPD

Thesis

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Chapter 1

General introduction

Introduction

The growing prevalence and clinical burden of chronic airways diseases such as bronchiectasis disease, asthma and COPD highlight the urgent need for a better understanding of disease mechanisms and more effective management strategies.

Chronic lung disease has always posed enormous health challenges globally, impacting millions of lives. Historically, bronchiectasis mostly occurred as a consequence of tuberculosis or other severe respiratory infections, which have been a primary cause of death and morbidity throughout all of premodern history. The author of this thesis has drawn inspiration from his personal experiences in the care for many patients with obstructive lung disease (COPD and asthma), infectious lung disease (including tuberculosis) and bronchiectasis disease, which is it at the intersection of the two. Other inspirations have been many works of art and literature. Particularly Thomas Mann's "The Magic Mountain" (Der Zauberberg) is striking for its depiction of the care for tuberculosis in the early 20th century, before the existence of effective antibiotic treatment and in the early days of X-ray diagnostics. This novel vividly illustrates the prolonged suffering and social isolation, and most of all the ineffectiveness of the management strategies of the time. While tuberculosis is no longer a major threat in the Western world, bronchiectasis disease still has much of the same inefficacy of the current spectrum of management, as well as little hope of true recovery. At the same time, COPD and asthma have taken prominence as the major challenges of our time in respiratory medicine. This historical context is crucial for understanding the current state of disease management, the ongoing challenge to offer our patients better care, and as the motivation for the research in this thesis.

Bronchiectasis: definition, pathogenesis and clinical implications

Bronchiectasis is characterized by abnormal and permanent dilation of the bronchi, meeting the diagnostic criteria outlined in the Fleischner Society definition, which includes a broncho-arterial ratio >1.0, lack of tapering of the bronchi, and visibility of airways within 1 cm of the pleura.[1] When this radiological abnormality is accompanied by symptoms such as cough, phlegm, and recurrent airway infections, it is called bronchiectasis disease. [2] Bronchiectasis disease is a chronic inflammatory condition that can arise from a variety of underlying disorders—such as post-infectious damage, immunodeficiencies, or connective tissue diseases—or without a clear underlying cause, most commonly categorized as idiopathic. The clinical presentation

can vary widely, ranging from mild cough and sputum production to frequent exacerbations and severe respiratory compromise.

Bronchiectasis disease can be further characterized as a muco-obstructive lung disease characterized by mucus obstruction and chronic inflammation. Other muco-obstructive lung diseases include chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), and primary ciliary dyskinesia (PCD)[3], as well as some asthma endotypes.[4] In muco-obstructive lung disease, impairments in the epithelial lining fluid homeostasis, increased secretion of mucins, or both, result in overly thick mucus.[5] This can lead to the adherence of mucus to the airway wall, the formation of mucus plaques and the inability to properly clear mucus via the mucociliary escalator. Thick mucus in smaller airways or dilated bronchiectatic airways can be difficult to expectorate. The presence of hyperconcentrated, static mucus plaques can lead to obstructed airflow, opportunities for colonization and chronic infection by pathogenic microorganisms, and a neutrophilic muco-inflammatory cycle.[6] This can result in (recurrent) bacterial exacerbations, progressive airway damage and remodeling, a disease mechanism captured in the 'vicious vortex' hypothesis of bronchiectasis disease.[7]

The epidemiology of bronchiectasis disease varies globally, with a notable prevalence in both developed and developing countries.[8, 9] Although comprehensive global data are scarce, studies suggest that the prevalence across different countries is around ~1% of the population and appears to be increasing, attributed in part to aging populations and improved diagnostics, most notably the increased use of chest CT scans.[10, 11] However, inclusion criteria for studies and diagnostic methods vary significantly, and the investigation of underlying diseases also differs. Consequently, prevalence data are inconsistent. The emergence of automated methods to objectively assess key features of structural lung disease in bronchiectasis may be one way to improve these estimates.

Figure 1. The 'vicious vortex' hypothesis of bronchiectasis. From: Flume PA, Chalmers JD, Olivier KN. Advances in bronchiectasis: endotyping, genetics, microbiome, and disease heterogeneity. Lancet. 2018 Sep;392(10150):880-890.

Radiological bronchiectasis: relationship with asthma and COPD

Notably, the presence of bronchiectatic airways is increasingly recognized as a complicating factor in the highly common airway diseases such as asthma and COPD. When radiological bronchiectasis is present in these diseases, it is often associated with more frequent exacerbations, increased airflow obstruction, and a substantial impact

on quality of life and prognosis.[12-14] This underscores the importance of early and accurate identification of ectatic airway changes.

Asthma is a highly prevalent lung disease affecting an estimated 262 million people worldwide.[15] Interestingly, it was shown in the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC)[16] cohort that 31% of bronchiectasis disease patient have a co-diagnosis of asthma.[9] Asthma is characterized by bronchial hypersensitivity and chronic inflammation of both the large and small (<2mm) airways [17, 18], typically with eosinophilic infiltration and upregulation of Th2-type cytokines, particularly IL-5, IL-4, IL-9, and IL-13. Recent research has highlighted a subgroup of asthma patients with radiologically significant mucus plugging on high-resolution CTs, characterized clinically by severe airflow obstruction and a lack of response to both bronchodilators and systemic glucocorticoids.[19]

COPD is even more prevalent than asthma, with an estimated 299 million people affected worldwide.[15] In the EMBARC cohort, a high percentage of 26% of bronchiectasis patients had a co-diagnosis of COPD.[9] Characteristic of COPD is persistent airflow obstruction due to lung damage secondary to chronic tobacco smoking or other inhaled substances.[20] Similar to asthma, in COPD there is airway inflammation of both the large and small airways [21, 22], with increased airway wall thickness associated with decreased airflow.[23] However, airway inflammation in COPD is typically neutrophilic, similar to bronchiectasis disease. Tobacco smoke exacerbates neutrophilic inflammation by inducing the release of proinflammatory cytokines and chemokines, increasing neutrophil recruitment and activation, and causing oxidative stress that further damages the airway epithelium and perpetuates the inflammatory response.[24, 25]

Shared symptoms and disease mechanisms

Bronchiectasis disease, asthma, and COPD share many symptoms and disease mechanisms. These include chronic airway inflammation with similar endotypes, airflow obstruction, airway remodeling, mucus hypersecretion and plugging, and colonization with pathogenic microorganisms such as *Pseudomonas aeruginosa*, *Aspergillus fumigatus*, or non-tuberculous mycobacteria. Some clinical phenotypes (e.g. bronchial hyperreactivity and 'frequent exacerbator') can also be recognized across all three conditions. These similarities can blur the distinction between the conditions, yet they can also serve as shared starting points for research questions and therapeutic interventions. Importantly, new methods of radiological evaluation can be used

to phenotype pathological airway changes with great precision irrespective of the diagnostic label.

Airway remodeling across diseases

Airway remodeling, which is characterized by structural changes in the airway wall, is driven by chronic inflammation and is a common feature of chronic airway diseases. [26-28] Airway wall changes include epithelial alterations, subepithelial fibrosis, goblet cell hyperplasia, basement membrane thickening, increased airway smooth muscle mass, and angiogenesis. This physiological response to injury may lead to persistently altered airway structure and function.[29] These changes contribute to airway narrowing, decreased lung function, and increased severity of symptoms. Airway wall thickening was shown to be an important determinant of airflow obstruction in pathological specimens of both asthma and COPD.[23, 30] Radiological measurements of airway wall thickening have also been linked to reduced airflow in both asthma and bronchiectasis [31, 32] as well as in COPD.[33]

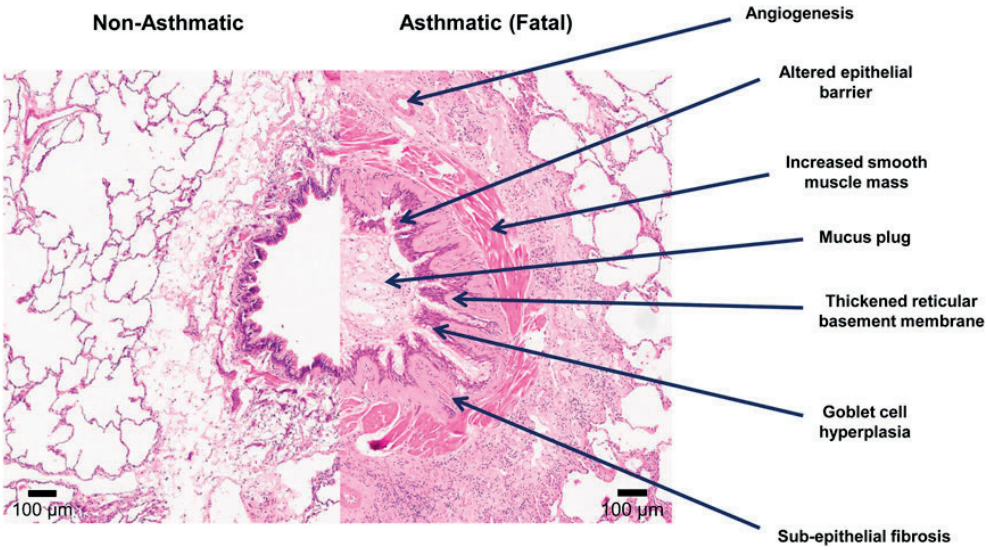

Figure 2. Airway cross-section showing diverse signs of airway remodeling.

From: Hsieh A, Assadinia N, Hackett TL. Airway remodeling heterogeneity in asthma and its relationship to disease outcomes. Front Physiol. 2023 Jan 19:14:1113100.

Mucus hypersecretion and plugging

Mucus hypersecretion, mucus plaque formation, and plugging are critical features in the pathogenesis of the aforementioned obstructive airway diseases, driven by chronic inflammation and an imbalance in mucin production and clearance. In bronchiectasis disease and COPD, mucus hypersecretion results from neutrophilic inflammation and an increase in mucin-producing cells (goblet cell hyperplasia), leading to thick, tenacious mucus that is difficult to clear. Mucus can stick to the airway wall and contribute to a reduction in the airway lumen and consequently a reduction in airflow. Furthermore, the formation of mucus plaques can create hypoxic conditions for the underlying airway epithelium, contributing to a mucoinflammatory positive feedback cycle.[3]

In COPD, chronic inflammation leads to structural changes, not only mucous gland hypertrophy but also loss of alveoli and narrowing and loss of small airways.[34] In airway samples from patients with COPD, higher concentrations of mucins have been reported in association with decreased rates of mucociliary clearance.[35] Recently, mucus plugs in COPD have been associated with decreased lung function and quality of life, and even with higher all-cause mortality.[36, 37] This was first demonstrated using visual counting of mucus plugs[36], but this method is time-consuming and prone to human inconsistency, limiting its practical adoption.

Mucus hypersecretion and mucus plugs have been recognized in the pathophysiology of asthma for over a hundred years, but more recently in relation to both mucus and blood eosinophil levels and radiological mucus scores.[19, 38] Elevated Charcot-Leyden crystal galectin messenger RNA in the sputum of patients with bronchiectasis and severe asthma underscores the role of eosinophilic inflammation, linking it to the pathophysiology of bronchial dilatation and mucus hypersecretion in these conditions.[39]

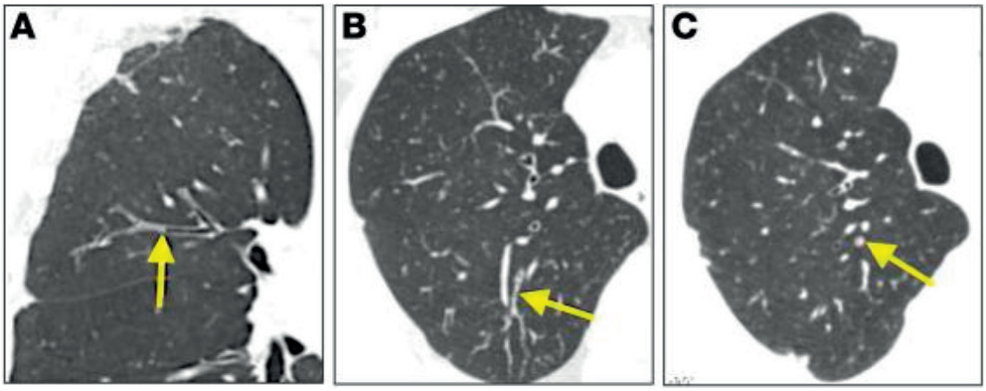

Figure 3. Mucus plugs as visualized on chest CT in asthmatic subjects. Mucus plug with branching (yellow arrow) seen in longitudinal section is identified as a tubular opacification (frontal plane). (B) Mucus plug with extensive branching seen in longitudinal section (transverse plane). (C) Mucus plug seen in cross-section is identified as rounded opacification (transverse plane). From: Dunican EM, Elicker BM, Gierada DS et al. Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction. J Clin Invest. 2018 Mar 1;128(3):997-1009.

Inflammatory endotypes: neutrophilic and eosinophilic

The inflammatory response in bronchiectasis, asthma, and COPD can be broadly categorized into neutrophilic or eosinophilic endotypes, reflecting the underlying immune mechanisms that can influence treatment choices.

In bronchiectasis disease, neutrophil activity, particularly neutrophil elastase, plays a central role. The formation of neutrophil extracellular traps (NETs) is linked to disease severity because high sputum levels of neutrophil elastase correlate with more severe disease manifestations and are associated with exacerbations and decrease with antibiotic treatment.[40] Both NETs and neutrophil elastase are under investigation as disease markers and therapeutic targets.[41] Importantly, high levels of active neutrophil elastase are associated with low microbiome diversity and specifically with *Pseudomonas aeruginosa* infection.[42]

Although neutrophilic inflammation is the most prevalent, an eosinophilic profile of bronchiectasis disease was identified in 22.6% of patients with blood eosinophil counts of ≥300 cells/µl.[43] From a pathophysiological viewpoint, eosinophils have also demonstrated elastolytic capacity and the secretion of substances that can damage the bronchial wall such as eosinophil cationic protein and metalloproteases.[44]

As known, eosinophils are the predominant type of inflammation in asthma. Eosinophils are also increasingly recognized as a distinct trait in COPD.[20, 45] Eosinophil levels are considered to predict response to steroid therapy and are used as the basis for the prescription of inhaled corticosteroids (ICS). In addition, with the emergence of specific biological medications, the use of these anti-inflammatory therapies to target eosinophils and associated Th2-response interleukins has been successful in the treatment of selected patients with (severe) asthma and COPD.[46, 47] Regarding the bronchial wall, intraepithelial eosinophils in the bronchial wall of asthma patients were associated with type 2 inflammation and bronchial hyperreactivity.[48] Manual CT measurements of the airway wall area (as a marker for wall thickness) of a few selected segmental bronchi were associated with sputum eosinophil counts and lower lung function in patients with eosinophilic asthma.[49]

Rationale for the current research: personalized medicine

Understanding the shared pathophysiological components of airway remodeling, mucus hypersecretion, and inflammatory endotypes underscores the need for a comprehensive approach to chronic airway diseases. The 'personalized medicine' paradigm aims to tailor interventions to the unique characteristics of each patient, considering factors such as genetic susceptibility, immunological profiles, microbiome, radiological markers, and environmental exposure. By moving beyond a one-size-fits-all approach, personalized strategies have the potential to improve treatment efficacy, minimize adverse effects, and optimize resource use in respiratory care, as well as research strategies. [50-52]

Bronchiectasis disease, with its variability in symptom severity, etiological mechanisms as well as its radiological features and extent of disease, appears to be particularly suited for a personalized medicine approach. The mechanisms behind the pathognomonic irreversible dilation of the airway and the great disease heterogeneity are still relatively poorly understood. Radiographic findings vary greatly among patients and are strongly influenced by the underlying cause, such as a severe past lung injury giving rise to limited, focal abnormalities and some systemic aetiologies and comorbidities showing more diffuse abnormalities. Until recently, no objective, quantitative measure of bronchiectasis has been widely adopted. Thus, both previous examples of either limited or diffuse abnormalities are grouped under the same label of 'bronchiectasis'. A systematic evaluation of the variety and extent of radiological abnormalities in a large cohort of bronchiectasis patients may improve our understanding of the heterogeneity and deepen our understanding of the links between disease, etiological factors and patient subgroups.

Automated radiological analysis

The increased use of chest CT scans for diagnosing and understanding chronic airways diseases also comes with the need for improved image analysis methods of these CTs.

A highly significant development is the emergence of automated tools for precise quantification of airway (and vascular) parameters on chest CT scans. By providing objective and reproducible measurements, clinicians can have objective biomarkers of airways disease activity and progression. Automated measurements are not only more consistent and objective than human radiological scoring, but they can also be much more sensitive, accurate and efficient. Without automation, the practical adoption of such measurements would likely remain limited to research settings and not suitable for clinical use.

An example of such an automated method is the bronchial-artery (BA) analysis, which can measure all bronchial and arterial dimensions across the bronchial tree. Different BA-ratios have been investigated as markers for bronchial widening and bronchial wall thickening. Using a traditional bronchiectasis definition of the outer dimension of a bronchus (B_{out}) being greater than that of the accompanying artery, different cut-offs of a B_{out}/A ratio of >1.5 or >1.1 can be used to calculate the percentage of enlarged airways. Additionally, bronchial wall thickness can be assessed using BA-ratios for wall thickness (B_{wt}/A) and the ratio of bronchial wall area to bronchial outer area (B_{wa}/B_{oa}). Interestingly, automated assessment of all visible BA-pairs on chest CTs has already been shown to be a sensitive method to detect airway wall thickening and airway widening in cystic fibrosis (CF) [53, 54] and pediatric asthma.[55]

Similar to automatic assessment of bronchial dimensions, the presence of mucus plugs across the bronchial tree can now also be investigated using fully automated algorithms. As mentioned before, in the past years studies have demonstrated the relationship between mucus plugs and lung function, symptoms and even all-cause mortality (in COPD), supporting the relevance of mucus plugs in chronic airways disease.[36, 37, 56] Algorithms can now automatically segment the bronchial tree, quantify the total number and volume of mucus plugs for the entire lung as well as for each individual bronchopulmonary segment.

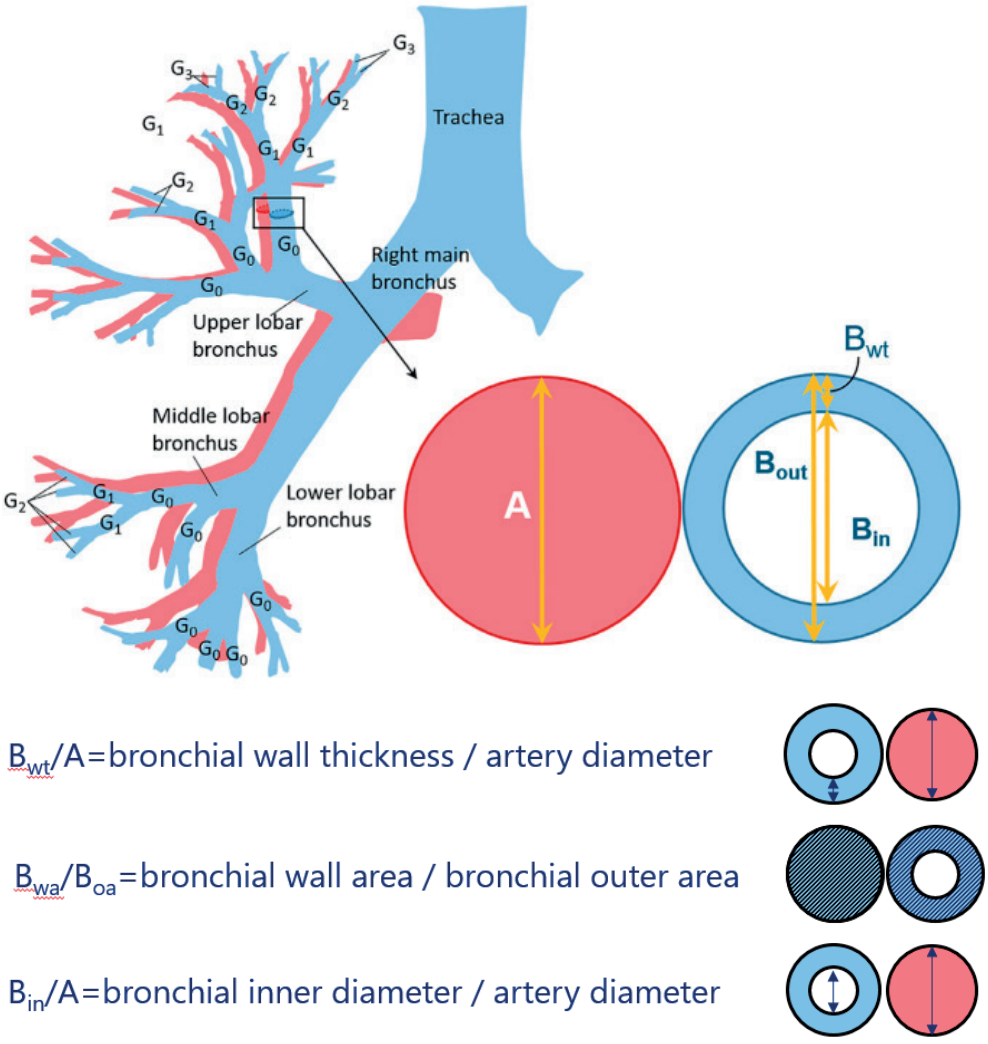

Figure 4. Schematic view of the bronchial tree and of a bronchus-artery (BA) pair in cross-section. The bronchial tree (blue) with its accompanying artery system (pink) is shown on the left. The segmental bronchi are defined as G0 and the subsegmental bronchi as G1. B_{out}: bronchial outer diameter, B_{in}: bronchial lumen diameter, B_{wt}: bronchial wall thickness, A: artery. From: Lv, Q, Gallardo-Estrella L, Andrinopoulou ER et al., *Automatic analysis of bronchus-artery dimensions to diagnose and monitor airways disease in cystic fibrosis.* Thorax. 2023 Dec 15;79(1):13-22.

Importantly, the use of such automated measurements can reveal airway changes which previously were not detected. While the traditional evaluation of bronchiectasis only highlights those airways which already acquired irreversible dilatation, quantitative markers of airway wall thickening and mucus plugging can signal airway inflammation potentially before the damage becomes irreversible, providing an opportunity for earlier intervention. If airway wall thickening and mucus plugging can be used as a surrogate for inflammatory activity, those patients can be identified who are most likely to benefit from anti-inflammatory interventions, antibiotic treatment, or intensified airway clearance. Integrating such quantitative CT analyses into clinical practice supports the move towards personalized medicine.

Anti-inflammatory therapies

Asthma and COPD have long been understood as conditions driven by chronic inflammation, while an inflammatory paradigm is also increasingly applied to bronchiectasis disease. The high prevalence of asthma, COPD and bronchiectasis as concomitant diagnoses, along with similarity in symptoms, has led to a high use of ICS and bronchodilator therapy in bronchiectasis, with over 50% of patients in the EMBARC cohort being prescribed these treatments.[9] As another example, 58% of the participants in the recent large ASPEN phase III trial were using inhaled corticosteroids at baseline.[57] However, this practice lacks proper justification, as there are no controlled studies supporting ICS or in combination with long-acting beta agonists (ICS/LABA) efficacy in bronchiectasis *alone*. The only double-blind comparison, which studied high-dose budesonide versus medium-dose budesonide-formoterol, indicated symptomatic benefits but lacked a placebo comparison.[58] A 2018 Cochrane review highlighted insufficient evidence to recommend ICS use in these patients.[59] Moreover, some data suggest potential downsides, including increased risks of exacerbations and hospitalizations.[60] To address this knowledge gap, randomized controlled studies are needed that focus on bronchiectasis disease patients without an asthma or COPD co-diagnosis.

While the broad use of ICS for managing chronic inflammation in bronchiectasis remains questionable, there is a much stronger rationale for employing targeted anti-Th2 therapies in cases of bronchiectasis driven by a clear Th2-mediated inflammatory response, such as in allergic bronchopulmonary aspergillosis (ABPA). These targeted therapies hold promise for improving clinical outcomes by addressing the specific Th2-inflammatory pathway involved. However, controlled studies investigating different biologicals in bronchiectasis disease have so far not been completed, although case series do show strong signs of efficacy.[61] Nonetheless, the potential for these treatments to

address specific inflammatory pathways aligns with the goals of personalized medicine, which seeks to tailor therapies to individual inflammatory profiles. More research into the efficacy of biologics in bronchiectasis could lead to more precise and effective treatment strategies.

Aims of this thesis

1. Radiological markers in bronchiectasis, asthma and COPD

This part explores how radiological signs such as airway dimensions, mucus plugs, and structural lung disease in bronchiectasis, asthma, and COPD are related to clinical characteristics. It aims to uncover the underlying mechanisms driving airway remodeling, obstruction, and disease progression through advanced imaging techniques and automated analyses. Understanding these relationships could identify potential markers for diagnosing airways disease, monitoring progression, therapy choices and risk assessment.

Research questions:

- What relationships exist between visually scored structural lung disease and clinical phenotype in bronchiectasis patients, and can these associations inform our understanding of disease heterogeneity and the necessity for individualized approaches? **(EMBARC BEST-CT study, chapter 2)**
- Can a fully automated bronchus-artery (BA) analysis quantify structural abnormalities in patients from a bronchiectasis clinical trial, and how do these metrics compare with visually scored semi-quantitative BEST-CT visual scoring and correlate with spirometry measures of airflow obstruction? **(iBEST CT study, chapter 3)**
- What insights can be gained from automatic analysis of structural lung abnormalities in a large cohort of bronchiectasis patients, and how can AI-based metrics enhance phenotyping and disease monitoring? **(EMBARC automated analysis study, chapter 4)**
- How do chest CT airway dimensions, mucus plugs, lung function, and eosinophilia interact in patients with bronchiectasis and an asthma co-diagnosis, and what does this imply about the pathophysiology and potential markers for disease severity? **(BASIIS study, chapter 5)**
- How does automated quantification of mucus plugs in COPD patients relate to clinical outcomes such as all-cause mortality, and what is the potential of such analyses for disease monitoring and risk stratification? **(COPDGene: automated mucus plugs analysis study, chapter 6)**

2. Impact of anti-inflammatory therapies on clinical outcomes

This part examines the role of anti-inflammatory therapies in managing chronic symptoms and changing disease courses in bronchiectasis with and without asthma. Clinical endpoints such as chronic cough and exacerbation frequency are evaluated after initiation of anti-inflammatory treatment, with the aim of guiding therapeutic interventions.

Research questions:

- What is the efficacy of combined beclomethasone-formoterol inhalation therapy in reducing chronic cough in non-CF bronchiectasis patients, and what implications does this have for clinical practice and the understanding of the role of inflammation in bronchiectasis symptoms? **(FORZA randomized controlled trial, chapter 7)**
- How does treatment with dupilumab affect exacerbation frequency and prednisone dosage in patients with allergic bronchopulmonary aspergillosis (ABPA) and asthma, and what does this reveal about the potential of biologic agents to modulate immune responses and improve clinical outcomes in ABPA. **(Dupilumab in ABPA case series, chapter 8)**

References

1. Bankier, A.A., et al., *Fleischner Society: Glossary of Terms for Thoracic Imaging.* Radiology, 2024. **310**(2): p. e232558.
2. Aliberti, S., 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, 2022. **10**(3): p. 298-306.
3. Boucher, R.C., *Muco-Obstructive Lung Diseases.* N Engl J Med, 2019. **380**(20): p. 1941-1953.
4. Most, J.F., *Muco-Obstructive Lung Diseases.* N Engl J Med, 2019. **381**(10): p. e20.
5. Kesimer, M., et al., *Airway Mucin Concentration as a Marker of Chronic Bronchitis.* N Engl J Med, 2017. **377**(10): p. 911-922.
6. Cole, P.J., *Inflammation: a two-edged sword--the model of bronchiectasis.* Eur J Respir Dis Suppl, 1986. **147**: p. 6-15.
7. Flume, P.A., J.D. Chalmers, and K.N. Olivier, *Advances in bronchiectasis: endotyping, genetics, microbiome, and disease heterogeneity.* Lancet, 2018. **392**(10150): p. 880-890.
8. Chandrasekaran, R., et al., *Geographic variation in the aetiology, epidemiology and microbiology of bronchiectasis.* BMC Pulm Med, 2018. **18**(1): p. 83.
9. Chalmers, J.D., et al., *Bronchiectasis in Europe: data on disease characteristics from the European Bronchiectasis registry (EMBARC).* Lancet Respir Med, 2023. **11**(7): p. 637-649.
10. O'Donnell, A.E., *Bronchiectasis - A Clinical Review.* N Engl J Med, 2022. **387**(6): p. 533-545.
11. Quint, J.K., et al., *Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study.* Eur Respir J, 2016. **47**(1): p. 186-93.
12. Perez-Miranda, J., L. Traversi, and E. Polverino, *Bronchiectasis in severe asthma: a distinct phenotype?* Curr Opin Pulm Med, 2019. **25**(1): p. 71-78.
13. Bendien, S.A., et al., *Bronchiectasis in Severe Asthma: Does It Make a Difference?* Respiration, 2020: p. 1-9.
14. Shi, L., et al., *Impact of Radiographic Bronchiectasis in COPD.* Respir Care, 2020. **65**(10): p. 1561-1573.
15. Diseases, G.B.D. and C. Injuries, *Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019.* Lancet, 2020. **396**(10258): p. 1204-1222.
16. Chalmers, J.D., et al., *The EMBARC European Bronchiectasis Registry: protocol for an international observational study.* ERJ Open Res, 2016. **2**(1).
17. Donovan, G.M. and P.B. Noble, *Small airways vs large airways in asthma: time for a new perspective.* J Appl Physiol (1985), 2021. **131**(6): p. 1839-1841.
18. Siora, A., et al., *Small airways in asthma: From inflammation and pathophysiology to treatment response.* Respir Med, 2024. **222**: p. 107532.
19. Dunican, E.M., et al., *Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction.* J Clin Invest, 2018. **128**(3): p. 997-1009.
20. Agusti, A., et al., *Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD Executive Summary.* Am J Respir Crit Care Med, 2023. **207**(7): p. 819-837.
21. Hogg, J.C., P.T. Macklem, and W.M. Thurlbeck, *Site and nature of airway obstruction in chronic obstructive lung disease.* N Engl J Med, 1968. **278**(25): p. 1355-60.
22. Saetta, M., et al., *CD8+ T-lymphocytes in peripheral airways of smokers with chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 1998. **157**(3 Pt 1): p. 822-6.
23. Tiddens, H.A., et al., *Cartilaginous airway dimensions and airflow obstruction in human lungs.* Am J Respir Crit Care Med, 1995. **152**(1): p. 260-6.

24. Piero, M., et al., *Remodeling in Response to Infection and Injury.* American Journal of Respiratory and Critical Care Medicine, 2001. **164**(supplement_2): p. S76-S80.
25. Stämpfli, M.R. and G.P. Anderson, *How cigarette smoke skews immune responses to promote infection, lung disease and cancer.* Nat Rev Immunol, 2009. **9**(5): p. 377-84.
26. Hirota, N. and J.G. Martin, *Mechanisms of airway remodeling.* Chest, 2013. **144**(3): p. 1026-1032.
27. An, S.S., et al., *Airway smooth muscle dynamics: a common pathway of airway obstruction in asthma.* Eur Respir J, 2007. **29**(5): p. 834-60.
28. Hsieh, A., N. Assadinia, and T.L. Hackett, *Airway remodeling heterogeneity in asthma and its relationship to disease outcomes.* Front Physiol, 2023. **14**: p. 1113100.
29. Kips, J.C. and R.A. Pauwels, *Airway wall remodelling: does it occur and what does it mean?* Clin Exp Allergy, 1999. **29**(11): p. 1457-66.
30. Chetta, A., et al., *Airways remodeling is a distinctive feature of asthma and is related to severity of disease.* Chest, 1997. **111**(4): p. 852-7.
31. Kim, J.H., et al., *Relationships Between High-Resolution Computed Tomographic Features and Lung Function Trajectory in Patients With Asthma.* Allergy Asthma Immunol Res, 2023. **15**(2): p. 174-185.
32. Yamamoto, Y., et al., *Impact of bronchial wall thickness on airflow obstruction in bronchiectasis.* Respir Physiol Neurobiol, 2022. **295**: p. 103788.
33. Mohamed Hoesein, F.A., et al., *Airway wall thickness associated with forced expiratory volume in 1 second decline and development of airflow limitation.* Eur Respir J, 2015. **45**(3): p. 644-51.
34. Xu, F., et al., *The molecular and cellular mechanisms associated with the destruction of terminal bronchioles in COPD.* Eur Respir J, 2022. **59**(5).
35. Anderson, W.H., et al., *The Relationship of Mucus Concentration (Hydration) to Mucus Osmotic Pressure and Transport in Chronic Bronchitis.* Am J Respir Crit Care Med, 2015. **192**(2): p. 182-90.
36. Diaz, A.A., et al., *Airway-Occluding Mucus Plugs and Mortality in Patients With Chronic Obstructive Pulmonary Disease.* JAMA, 2023. **329**(21): p. 1832-1839.
37. Okajima, Y., et al., *Luminal Plugging on Chest CT Scan: Association With Lung Function, Quality of Life, and COPD Clinical Phenotypes.* Chest, 2020. **158**(1): p. 121-130.
38. Dunnill, M.S., *The pathology of asthma, with special reference to changes in the bronchial mucosa.* J Clin Pathol, 1960. **13**(1): p. 27-33.
39. Frossing, L., A. Von Bulow, and C. Porsbjerg, *Bronchiectasis in severe asthma is associated with eosinophilic airway inflammation and activation.* J Allergy Clin Immunol Glob, 2023. **2**(1): p. 36-42.
40. Keir, H.R., et al., *Neutrophil extracellular traps, disease severity, and antibiotic response in bronchiectasis: an international, observational, multicohort study.* Lancet Respir Med, 2021. **9**(8): p. 873-884.
41. Chalmers, J.D., et al., *Phase 2 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis.* N Engl J Med, 2020. **383**(22): p. 2127-2137.
42. Oriano, M., et al., *Sputum neutrophil elastase associates with microbiota and Pseudomonas aeruginosa in bronchiectasis.* Eur Respir J, 2020. **56**(4).
43. Shoemark, A., et al., *Characterization of Eosinophilic Bronchiectasis: A European Multicohort Study.* Am J Respir Crit Care Med, 2022. **205**(8): p. 894-902.
44. Guan, W.J., et al., *Significance and Potential Role of Eosinophils in Non-Cystic Fibrosis Bronchiectasis.* J Allergy Clin Immunol Pract, 2023. **11**(4): p. 1089-1099.
45. David, B., et al., *Eosinophilic inflammation in COPD: from an inflammatory marker to a treatable trait.* Thorax, 2021. **76**(2): p. 188-195.
46. Agache, I., et al., *Efficacy and safety of treatment with biologicals (benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) for severe eosinophilic asthma. A systematic review for the*

EAACI Guidelines - recommendations on the use of biologicals in severe asthma. Allergy, 2020. **75**(5): p. 1023-1042.
47. Donovan, T., et al., *Anti-IL-5 therapies for chronic obstructive pulmonary disease.* Cochrane Database Syst Rev, 2020. **12**(12): p. CD013432.
48. Al-Shaikhly, T., et al., *Location of eosinophils in the airway wall is critical for specific features of airway hyperresponsiveness and T2 inflammation in asthma.* Eur Respir J, 2022. **60**(2).
49. Inoue, H., et al., *CT-assessed large airway involvement and lung function decline in eosinophilic asthma: The association between induced sputum eosinophil differential counts and airway remodeling.* J Asthma, 2016. **53**(9): p. 914-21.
50. Martins, M., H.R. Keir, and J.D. Chalmers, *Endotypes in bronchiectasis: moving towards precision medicine. A narrative review.* Pulmonology, 2023. **29**(6): p. 505-517.
51. Schoettler, N. and M.E. Strek, *Recent Advances in Severe Asthma: From Phenotypes to Personalized Medicine.* Chest, 2020. **157**(3): p. 516-528.
52. Brightling, C. and N. Greening, *Airway inflammation in COPD: progress to precision medicine.* Eur Respir J, 2019. **54**(2).
53. Chen, Y., et al., *Automatic bronchus and artery analysis on chest computed tomography to evaluate the effect of inhaled hypertonic saline in children aged 3-6 years with cystic fibrosis in a randomized clinical trial.* J Cyst Fibros, 2023.
54. Lv, Q., et al., *Automatic analysis of bronchus-artery dimensions to diagnose and monitor airways disease in cystic fibrosis.* Thorax, 2023.
55. van den Bosch, W.B., et al., *Children with severe asthma have substantial structural airway changes on computed tomography.* ERJ Open Res, 2024. **10**(1).
56. Dunican, E.M., et al., *Mucus Plugs and Emphysema in the Pathophysiology of Airflow Obstruction and Hypoxemia in Smokers.* Am J Respir Crit Care Med, 2021. **203**(8): p. 957-968.
57. Information, I.I.M., *ASPEN Study: Phase 3 Study to Assess the Efficacy, Safety, and Tolerability of Brensocatib in Participants with Non-Cystic Fibrosis Bronchiectasis*. 2024.
58. Martinez-Garcia, M.A., et al., *Clinical efficacy and safety of budesonide-formoterol in non-cystic fibrosis bronchiectasis.* Chest, 2012. **141**(2): p. 461-468.
59. Kapur, N., et al., *Inhaled corticosteroids for bronchiectasis.* Cochrane Database Syst Rev, 2018. **5**(5): p. CD000996.
60. Polverino, E., et al., *Inhaled corticosteroids use in patients with bronchiectasis: Data from the EMBARC registry.* European Respiratory Journal, 2021. **58**(suppl 65): p. OA1312.
61. Oriano, M., et al., *T2-High Endotype and Response to Biological Treatments in Patients with Bronchiectasis.* Biomedicines, 2021. **9**(7).

Part I

Imaging and Quantification

Chapter 2

Structural Lung Disease and Clinical Phenotype in Bronchiectasis Patients: The EMBARC CT Study

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Abstract

Rationale: Chest computed tomography (CT) scans are essential to diagnose and monitor bronchiectasis (BE). To date, few quantitative data are available about the nature and extent of structural lung abnormalities (SLAs) on CT scans of patients with BE. **Objectives:** To investigate SLAs on CT scans of patients with BE and the relationship of SLAs to clinical features using the EMBARC (European Multicenter Bronchiectasis Audit and Research Collaboration) registry. **Methods:** CT scans from patients with BE included in the EMBARC registry were analyzed using the validated Bronchiectasis Scoring Technique for CT (BEST-CT). The subscores of this instrument are expressed as percentages of total lung volume. The items scored are atelectasis/consolidation, BE with and without mucus plugging (MP), airway wall thickening, MP, ground-glass opacities, bullae, airways, and parenchyma. Four composite scores were calculated: total BE (i.e., BE with and without MP), total MP (i.e., BE with MP plus MP alone), total inflammatory changes (i.e., atelectasis/consolidation plus total MP plus ground-glass opacities), and total disease (i.e., all items but airways and parenchyma). **Measurements and Main Results:** CT scans of 524 patients with BE were analyzed. Mean subscores were 4.6 (range, 2.3-7.7) for total BE, 4.2 (1.2-8.1) for total MP, 8.3 (3.5-16.7) for total inflammatory changes, and 14.9 (9.1-25.9) for total disease. BE associated with primary ciliary dyskinesia was associated with more SLAs, whereas chronic obstructive pulmonary disease was associated with fewer SLAs. Lower FEV_1, longer disease duration, *Pseudomonas aeruginosa* and nontuberculous mycobacterial infections, and severe exacerbations were all independently associated with worse SLAs. **Conclusions:** The type and extent of SLAs in patients with BE are highly heterogeneous. Strong relationships between radiological disease and clinical features suggest that CT analysis may be a useful tool for clinical phenotyping.

Introduction

Bronchiectasis disease is a clinical syndrome characterized by cough, sputum production and recurrent infectious exacerbations combined with the radiological appearance of abnormal dilatation of the bronchi [1]. Bronchiectasis disease may result secondary to a variety of etiologies and is highly heterogeneous in its clinical, microbiological and functional attributes. The irreversible dilatation of bronchi is assumed to reflect accumulated structural airway damage and is associated with chronic inflammation, bacterial infection, impaired mucociliary clearance and disease progression, known as the concept of the 'vicious vortex' [2].

Assessment and management are based on clinical assessment of disease severity and disease activity. The frequency of exacerbations, extent of symptoms and the presence of airway infections such as *Pseudomonas aeruginosa* (PsA) can be used to identify patients at higher risk of future poor outcomes. Composite clinical scores, such as the bronchiectasis severity index, combine a number of clinical factors to identify patients at higher risk of exacerbations, hospitalisations and mortality.

Bronchiectasis is defined by the presence of radiological abnormalities, but currently, the extent of radiological disease is not routinely considered when evaluating patient's phenotype or assessing their risk.

The gold standard for the radiological diagnosis of bronchiectasis is thin-section chest computed tomography (CT) scans. Morphologic criteria for bronchiectasis on CT-scans are bronchial dilatation relative to the accompanying pulmonary artery, lack of tapering of the bronchus, and identification of bronchi within 1 cm of the pleural surface, often accompanied by bronchial wall thickening and mucus plugging [3]. However, in routine clinical practice airway abnormalities are evaluated subjectively and no quantification of bronchiectasis or accompanying features is routinely performed.

For the quantitative analysis of airway and parenchymal abnormalities in bronchiectasis disease, the Bronchiectasis Scoring Technique for CT (BEST-CT) was developed. BEST-CT is a scoring system using morphometric principles that has been shown to be effective in detecting and monitoring the extent of airway abnormalities as a percentage of the affected parenchyma. BEST-CT has been shown to be a reproducible system to quantify the severity and extent of the structural lung abnormalities in patients with Granulomatous Lymphocytic Interstitial Lung Disease and bronchiectasis patients chronically infected with PsA [4-7].

The European Multi-center Bronchiectasis Audit and Research Collaboration (EMBARC) registry was established in 2015 [8] as a prospective, pan-European observational study of bronchiectasis patients [9]. As BEST-CT is currently the best validated scoring method to quantify extent of radiological disease in bronchiectasis, we hypothesized that radiological data would be associated with clinical phenotype. We conducted a sub-study embedded within the EMBARC registry to incorporate quantitative CT analysis in more than 500 patients with the aim of establishing relationships between radiological extent of disease and its etiology, severity and phenotype.

Materials and methods

Study population

We collected clinical data and CTs and from patients enrolled in the EMBARC registry. Details of the EMBARC data collection protocol and baseline data from the EMBARC registry have been published previously [8, 9]. Key inclusion criteria for patients to be included in the EMBARC registry are: patients with a primary clinical diagnosis of bronchiectasis consisting of (1) a clinical history consistent with bronchiectasis and (2) CT scan demonstrating bronchiectasis were included in the registry, per judgment of the including center. Key exclusion criteria for EMBARC registry are (1) bronchiectasis due to known cystic fibrosis, (2) age < 18 years and (3) patients who are unable or unwilling to provide informed consent. A complete list of in- and exclusion criteria was described previously [8]. For the current substudy, 8 bronchiectasis centers in 6 countries were included: Rotterdam, The Netherlands; Dundee, London and Cambridge, UK; St Niklaas, Belgium; Monza, Italy; Haifa, Israel; and Paris, France [Figure 1]. Each center was asked to make a completely random sub selection (50-100 patients) within their available cohort. In parallel to the primary bronchiectasis registry, EMBARC has a European non-tuberculous mycobacterial (NTM) registry substudy, which collects additional data from patients meeting the IDSA/ATS criteria for NTM active infection [10]. The NTM registry was used to enrich the cohort for patients with active NTM infection. This oversampling was performed to ensure sufficient statistical power to investigate this relevant clinical determinant (NTM) with a relatively low prevalence in European centers [11].

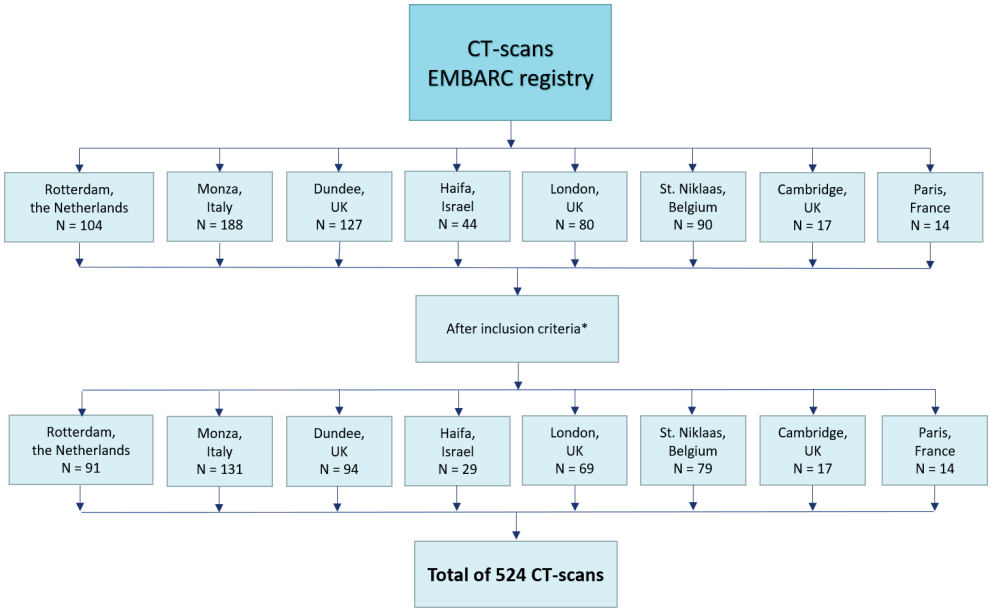

Figure 1. Flow chart CT selection

This figure represents the flowchart of the eligible scans (N) used for BronchiEctasis Scoring Technique for Computed Tomography (BEST-CT) from the European Multi-center Bronchiectasis Audit and Research Collaboration (EMBARC) registry.

*: (1) inspiratory chest CT series; (2) continuous helical CT acquisition; (3) slice thickness equal or less than 1.5mm; (4) imaging of the entire lung parenchyma; and (5) no major artifacts or mild artifacts present with minimal effect on visualization of the airways. Moreover, for each patient the centers selected the chest CT-scan that was performed closest to the time of enrolment in the EMBARC cohort (with a maximum interval of +/- 4 year, 1460 days).

CT = computed tomography; NTM = Non tuberculous mycobacteria; UK = United Kingdom.

Clinical parameters

The following data was collected from the EMBARC registry: demographics, previous medical history, comorbidities, spirometry, hospital admissions in the year prior to inclusion in the study, microbiology and severity of disease as reflected by the Bronchiectasis Severity Index (BSI) and FACED score [12, 13]. Detailed definitions of the baseline data are available in the supplementary material (supplement S1).

The underlying etiology of bronchiectasis is recorded in the EMBARC registry based on testing recommendations by European Respiratory Society guidelines. Ten different etiology groups were defined based on the available categories in the registry and the sample sizes per group: (1) idiopathic bronchiectasis; (2) allergic bronchopulmonary aspergillosis (ABPA); (3) asthma; (4) primary/secondary immunodeficiency (5)

connective tissue disease, rheumatoid arthritis (RA) and inflammatory bowel disease; (6) chronic obstructive pulmonary disease (COPD); (7) NTM infection; (8) other disease (including Mounier-Kuhn syndrome, yellow nail syndrome, Young's syndrome, CFTR-related disorders, aspiration and gastroesophageal reflux disease); (9) post infectious bronchiectasis (including post tuberculosis); and (10) primary ciliary dyskinesia (PCD).

Additionally, this study investigates whether patients have a co-diagnosis of asthma and/or COPD in addition to the recorded primary etiology of the bronchiectasis

In the EMBARC registry, patients were categorized by their duration of bronchiectasis disease in 5 different groups (0-5 years; 5-10 years; 10-15 years; 15-20 years and ≥20 years). Hospital admissions due to pulmonary exacerbations in the last year were categorized as: none, one, or two or more. Furthermore, patients were categorized by blood eosinophil counts, either normal or elevated (≥300 cells/mL) [14] .

CT collection

The Erasmus MC LungAnalysis core laboratory (Rotterdam, the Netherlands) provided participating centers with a procedure to verify the pseudonymity of CT images and facilitated safe data transfer of pseudonymized CT scans from participating hospitals to LungAnalysis. CT scans were included in this study if they fulfilled the following requirements: (1) correct digital format (correct DICOM headers), (2) sufficient inspiratory lung volume as defined by a round shape of the trachea and presence of lung parenchyma between the heart and sternum, (3) complete display of the lungs, (4) no artifacts or mild artifacts with minimal effect on the visualization of the lungs [Figure 1]. Moreover, for each patient the centers selected the chest CT-scan that was performed closest to the time of enrolment in the EMBARC cohort (with a maximum interval of +/- 4 year, 1460 days).

BEST-CT scoring

BEST-CT is a morphometric scoring system based upon the same principles as the extensively validated Perth-Rotterdam Annotated Grid Morphometric Analysis for CF (PRAGMA-CF)[6, 15]. In short: a grid is placed on 10 equally spaced axial chest-CT slices between lung apex and base, based on PRAGMA-CF scoring method [15, 16]. Each grid box is annotated by a trained and certified observer for the presence of structural lung abnormalities [5]. Each grid cell that contains at least 50% coverage of the lung is scored using the following hierarchical system (highest to lowest priority): 1. Atelectasis/consolidation (ATCON), 2. bronchiectasis with mucous plugging (BEMP), 3. bronchiectasis without mucous plugging (BEwMP), 4. Airway wall thickening (AWT), 5. Mucous plugging without bronchiectasis (MP), 6. Ground-glass opacities

(GGO), 7. Bullae (BUL), 8. Airways (A)(all airways which are not dilated) and 9. Parenchyma (P) (Parenchyma without annotated abnormalities) [Figure 1].

The following composite BEST-CT scores were used to investigate the relation between clinical outcomes and CT findings:

- Total bronchiectasis (%TBE) = %BEMP + %BEwMP
- Total mucus plugging (%TMP) = %BEMP + %MP
- Total of inflammatory CT-characteristics (%TInF) = %ATCON + %BEMP + %MP + %GGO
- Total disease (%DIS) = %ATCON + %TBE + %AWT + %MP + %GGO + %BUL

Intra- and inter-observer reliability

Certification was obtained by completion of standardized training modules (CF-CT, PRAGMA-CF and BEST-CT). The observer who scored all CT scans was a radiology resident with subspecialty training in thoracic radiology (AvB). The second observer for the inter-observer reliability was a certified LungAnalysis laboratory staff (M.B.). To assess intra-observer variability of the BEST-CT scoring method the main observer rescored 28 randomly selected CTs, one month after completion.

Statistical analysis

Descriptive statistics of patient characteristics are displayed as median [interquartile range] or percentage, as appropriate. Intra- and inter-observer agreement of CT scoring methods, intra-class correlation coefficients (ICC) were calculated with two-way mixed-effects models, assessing consistency of single measurements. ICC values <0.50 were considered poor, 0.50-0.75 moderate, 0.75-0.90 good, and >0.90 excellent [17].

To investigate the association between the 4 different BEST-CT composite scores (%TBE, %MP, %TinF, %DIS) and clinical parameters (age, gender, length of disease FEV_1 %pred, microbiology, smoking status, hospital admissions, etiology, co-diagnosis of asthma and/or COPD, eosinophil count, BSI and FACED) we used multivariable linear regression. For categories we also performed F-test for overall effects. All statistical analysis was done using SPSS version 27.0 (SPSS Inc., Chicago, IL) and statistical software package R, version 4.0.5 (R Foundation for Statistical Computing. Vienna, 2005). Additional analyses that did not show any significant results are not shown. Correction for multiple testing was not performed. Statistically significant results were defined as a p-value less than 0.05.

Results

CT Collection and study population

In total, 664 CT scans were collected from the 8 participating centers. Out of these, 140 CT scans were excluded (as illustrated in Figure 1). Hence 524 inspiratory scans were analyzed using the BEST-CT method. The median time between CT scan and enrollment in the EMBARC registry was 210 days [interquartile range (IQR) 80-560 days]. Patient characteristics and etiology of bronchiectasis disease are shown in table1. 63% of patients were female (N=329) and median age was 66 years [IQR 55-74]. In the majority of cases, the cause of bronchiectasis was attributed to idiopathic and post-infectious etiology: in 37% (n = 193) and 14% (n = 76), respectively (Table 1). 35% of the patients had an infection with PsA and 19% with active NTM infection.

Table 1. Patient characteristics

Demographics	Value
Number of analyzed CT scans	524
Age (Years)	66 [55 – 74]
Gender (Male/Female)	135 (37) / 329 (63)
BMI	23.4 [w] [20.5-27.6]
Country	
Rotterdam, The Netherlands	91 (17)
St Niklaas, Belgium	79 (15)
London, United Kingdom	69 (13)
Dundee, United Kingdom	94 (18)
Cambridge, United Kingdom	17 (3)
Haifa, Israel	29 (6)
Monza, Italy	131 (25)
Paris, France	14 (3)
History of Bronchiectasis[x]	
< 5 years	237 (48)
5 – 9 years	87 (18)
10-14 years	55 (11)
15-20 years	30 (6)
>20 years	86 (17)
Underlying Etiology	
Idiopathic	193 (37)
Post Infective	76 (14)
Other diseases	52 (10)
ABPA	35 (7)
Primary/secondary immunodeficiency	35 (7)

Table 1. Continued

Demographics	Value
NTM	32 (6)
COPD	29 (5)
Primary Ciliary Dyskinesia	26 (5)
CTD / RA / IBD	25 (5)
Asthma	20 (4)
Co-diagnosis of Asthma and/or COPD	212 (40.5)
Asthma	138 (26)
COPD	95 (18)
Hospital admissions in the last year[q]	
0	396 (76)
1	100 (19)
> 2	28 (5)
Spirometry	
FEV_1, %pred	79% [64 – 98%]

Spectrum of Chest CT outcomes

Table 2 presents the median and IQR of each component score, and of the composite scores %TBE, %TMP, %TinF, and %DIS. Also the prevalence of patients with any cells scored positive on that particular component is reflected in the table. Although most of the scans showed components of bronchiectasis (BEMP and/or BEwMP) and infection/inflammation (BEMP, MP, ATCON, GGO), there was a wide spread in the extent in which these abnormalities were present. %TBE ranged from 0 (in 20 patients) to 23%, %MP from 0 to 59%, %TinF from 0 to 60%, and %DIS from 0 to88%. Outcomes of the CT scans per patient are shown in a stacked-bar graph of all component scores, demonstrating the heterogeneity of the extent of the different types of structural lung abnormalities across all patients (Figure 2).

BEST-CT and clinical characteristics

Table 3 shows the results of the multiple regression analysis for BEST-CT composite scores (%TBE, %TMP, %TinF, and %DIS) with the clinical characteristics. Several clinical characteristics were significantly associated with the BEST-CT composite scores. Older patients and those with a longer duration of disease (especially a length of 15-20 years) had significantly more radiological changes on the CT scan for all composite scores ($p < 0.01$) except %TMP vs age ($p = 0.17$).

Overall, bronchiectasis etiology was significantly associated with all BEST-CT composite scores ($p < 0.01$). Patients with NTM specified as the etiology of their bronchiectasis had significantly higher %TinF, and %DIS scores. PCD was significantly

Table 2. Component and composite scores BEST-CT

	Median	IQR	Prevalence (%)
Component scores			
%ATCON	1.89	0.71 – 4.42	95
%BEMP	0.48	0.00 – 1.77	74
%BEwMP	3.68	1.47 – 6.13	95
%AWT	0.41	0.00 – 2.10	58
%MP	3.31	0.45 – 9.35	87
%GGO	0.00	0.00 – 0.16	34
%BUL	0.00*	0.00 – 0.00	18
%A	0.00	0.00 – 0.29	31
%P	85.10	73.89 – 90.35	100
Composite scores			
%TBE	4.69	2.32 – 7.66	96
%TMP	4.21	1.12 – 10.91	89
%TinF	8.31	3.54 – 16.68	99
%DIS	14.88	9.19 – 25.86	99

This table presents the median, interquartile ranges [IQR] of patients with a > 0 BronchiEctasis Scoring Technique for Computed Tomography (BEST-CT) component and composite scores. The third column represents the prevalence of patients with any cells scored positive for that particular component score. The order of components follows the hierarchical order by which the components are scored. ATCON = Atelectasis and/or consolidation; BEMP = Bronchiectasis with mucus plugging. BEwMP = Bronchiectasis without mucus plugging; AWT = airway wall thickening. MP = Mucus plugging; GGO = Ground-glass opacities. BUL = bullae. A = Airways. P = Parenchyma (without annotated abnormalities). TBE = Total bronchiectasis. TMP = Total mucus plugging. TinF = Total inflammatory features. DIS = Total disease. All BEST-CT subscores are expressed in % of total lung volume. *As BUL were present in relatively few CT-scans (n = 93), the median and IQR are 0.00.

associated with more %TMP and %TinF. ABPA and post-infectious aetiologies of bronchiectasis on the other hand were significantly associated with a higher %TBE. However, patients with primary and/or secondary immunodeficiency, or COPD as the underlying cause of bronchiectasis had significantly lower %TBE. A co-diagnosis of asthma and/or COPD was also negatively associated with %TBE. The sample size was large enough to allow us to statistically check for interaction between the variables sex and asthma/COPD co-diagnosis, but this did not show any evidence for differences in the effect size between males and females on %TBE, or any of the other composite outcome scores (data not shown).

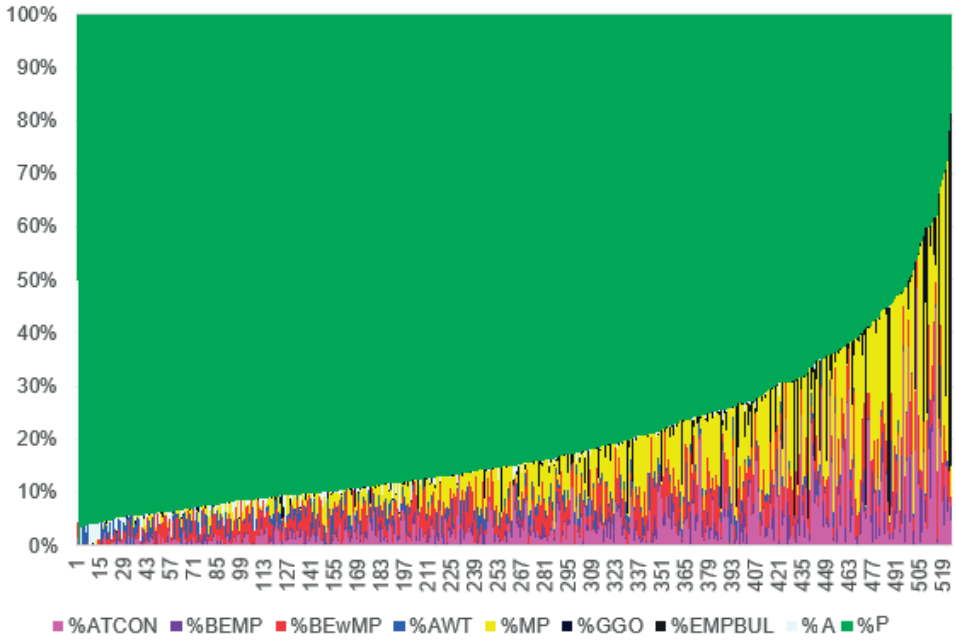

Figure 2. Visual distribution of the EMBARC population.

This stacked bar chart shows the results of BronchiEctasis Scoring Technique for Computed Tomography (BEST-CT) scoring of 524 chest computed tomography (CT) scans. Each stacked bar represents the analysis results of one CT scan. Component scores are expressed as percentage of total lung volume and add up to 100% on the Y-axis. On the X-axis patients are represented (n = x)

Subscores in the order by which they are scored. ATCON = Atelectasis and/or consolidation; BEMP = Bronchiectasis with mucus plugging. BEwMP = Bronchiectasis without mucus plugging; AWT = airway wall thickening. MP = Mucus plugging; GGO = Ground-glass opacities. BUL = bullae. A = Airways. P = Parenchyma). Patients are sorted based on the total disease score (%DIS) = %ATCO + %TBE + %AWT + %MP + %GGO + %BUL.

For patients with active NTM infection, all composite scores were significant higher (p-value varying between 0.02 - <0.01). In patients with a positive PsA isolation, %TBE (p <0.01) and %TMP (p = 0.02) scores were significantly increased.

All BEST-CT composite scores showed an inverse association with FEV_1 % predicted values (p = <0.01). Both clinical severity scores (BSI and FACED) had a strong positive association with %TBE, %TMP, %TinF and %DIS (p < 0.01).

%TinF and %DIS were associated with hospital admissions for a severe exacerbation, especially one hospital admission was significant correlated with these two composite

Table 3. Multiple regression analysis BEST-CT

		%TBE		%TMP		%TinF		%DIS	
		E [SE]	**p-value**	**E [SE]**	**p-value**	**E [SE]**	**p-value**	**E [SE]**	**p-value**
Model 1	**Age**	0.01 [0.00]	0.0018*	0.00 [0.00]	0.17	0.02 [0.00]	<0.0001*	0.02 [0.00]	<0.0001*
	Gender (Female)	-0.03 [0.09]	0.72	0.15 [0.15]	0.30	- 0.02 [0.14]	0.88	-0.02 [0.14]	0.85
	Length of disease to enrolment		<0.0001*^		<0.0001*^		<0.0001*^		<0.0001*^
	0 – 5 years	ref		ref		ref		ref	
	5 – 9 years	0.19 [0.12]	0.10	0.05 [0.19]	0.80	-0.17 [0.18]	0.35	-0.12 [0.18]	0.51
	10-14 years	0.27 [0.14]	0.06	0.17 [0.23]	0.45	0.11 [0.22]	0.60	0.16 [0.22]	0.46
	15-20 years	0.63 [0.19]	0.0008*	1.12 [0.30]	0.0003*	1.09 [0.29]	0.0002	0.87 [0.29]	0.003*
	>20 years	0.29 [0.13]	0.02*	0.07 [0.20]	0.74	0.07 [0.20]	0.72	0.08 [0.19]	0.68
	FEV_1, %pred	-0.68 [0.16]	0.0007*	-2.37 [0.27]	<0.0001*	-2.60 [0.26]	<0.0001*	-2.46 [0.26]	<0.0001*
	Microbiology								
	PsA isolation	0.28 [0.09]	0.002*	0.34 [0.15]	0.02*	0.14 [0.14]	0.31	0.13 [0.14]	0.34
	NTM isolation	0.34 [0.12]	0.006*	0.65 [0.20]	0.001*	0.43 [0.19]	0.02*	0.45 [0.19]	0.02*
	Smoking status		0.34^		0.82^		0.28^		0.19^
	Never	Ref		Ref		Ref		Ref	
	Ex	0.01 [0.09]	0.89	0.05 [0.15]	0.74	0.12 [0.15]	0.41	0.20 [0.14]	0.17
	Current	-0.30 [0.16]	0.06	-0.11 [0.25]	0.66	-0.20 [0.24]	0.42	-0.00 [0.24]	0.99
	Hospital Admissions		0.50^		0.70^		0.008*^		0.002*^
	0	Ref		Ref		Ref		Ref	
	1	0.10 [0.10]	0.33	0.12 [0.17]	0.48	0.48 [0.17]	0.004*	0.53 [0.16]	0.001*
	≥2	0.00 [0.19]	0.99	0.23 [0.30]	0.44	0.54 [0.29]	0.06	0.54 [0.29]	0.06
	Etiology		<0.0001*^		<0.0001*^		<0.0001*^		0.0003*^
	Idiopathic	Ref		Ref		Ref		Ref	
	ABPA	0.40 [0.18]	0.03*	0.15 [0.30]	0.62	0.25 [0.28]	0.38	0.29 [0.29]	0.31
	Asthma	0.10 [0.23]	0.66	-0.52 [0.37]	0.16	-0.53 [0.35]	0.13	-0.57 [0.35]	0.10

Table 3. Continued

		%TBE		%TMP		%TinF		%DIS	
		E [SE]	**p-value**	**E [SE]**	**p-value**	**E [SE]**	**p-value**	**E [SE]**	**p-value**
	Primary/secondary immunodeficiency	-0.40 [0.17]	0.02*	-0.33 [0.28]	0.24	-0.44 [0.27]	0.10	-0.29 [0.27]	0.29
	CTD / RA / IBD	0.10 [0.19]	0.58	-0.15 [0.31]	0.63	0.00 [0.29]	0.98	0.28 [0.30]	0.35
	COPD	-0.40 [0.20]	0.05*	-0.56 [0.33]	0.09	-0.46 [0.31]	0.15	-0.11 [0.31]	0.72
	NTM	-0.03 [0.21]	0.89	0.53 [0.33]	0.11	0.69 [0.32]	0.03*	0.66 [0.31]	0.04*
	Other diseases	-0.05 [0.15]	0.74	-0.04 [0.23]	0.86	0.43 [0.23]	0.06	0.38 [0.22]	0.08
	Post Infective	-0.37 [0.12]	0.003*	0.25 [0.20]	0.21	0.15 [0.19]	0.44	-0.03 [0.19]	0.85
	PCD	0.26 [0.20]	0.20	0.78 [0.33]	0.02*	0.69 [0.32]	0.03*	0.48 [0.31]	0.12
	Co-diagnosis of Asthma and/or COPD	-0.24 [0.10]	0.01*	-0.19 [0.16]	0.25	-0.26 [0.53]	0.09	-0.26 [0.15]	0.08
	Elevated blood eosinophil count	-0.00 [0.14]	0.99	0.16 [0.23]	0.47	0.54 [0.29]	0.44	-0.09 [0.21]	0.68
Model 2	**BSI**	0.05 [0.00]	<0.0001*	0.10 [0.02]	<0.0001*	0.14 [0.02]	<0.0001*	0.13 [0.02]	<0.0001*
Model 3	**FACED**	0.17 [0.03]	<0.0001*	0.32 [0.04]	<0.0001*	0.42 [0.04]	<0.0001*	0.41 [0.04]	<0.0001*

This table shows multivariable linear regression for patient characteristics versus composite scores of BronchiEctasis Scoring Technique for Computed Tomography (BEST-CT). Results are present in multiple linear regression as Estimate (E) with Standard Error [ER] and p-value. For categories we also preformed F-test for overall effects and present only as p-value*. Only if F-test for overall effect for categories are significant the P-values are reported for multiple linear regression.

Reference value (Ref) where chosen for categories: for gender – female; for history of bronchiectasis - <5 years; for smoking status – never; for Blood eosinophil count – normal tested; for underlying etiology – idiopathic.

A total of 498 patients (model 1) were analysed in the main multiple linear regression analysis. However, BSI (model 2, total of 518 patients) and FACED (model 3, total of 492 patients) were put into different models (without there composite scores) to avoid co-linearity.

Model 1 (main model) consist of age, length of disease, gender, underlying etiology, co-diagnosis of Asthma and/or COPD, smoking status, FEV1 %predicted, PA infection, NTM infection, hospital admissions, and blood eosinophil count.

Model 2 consist of age, length of disease, gender, underlying etiology, co-diagnosis of Asthma and/or COPD, smoking status, blood eosinophil count and BSI

Model 3 consist of age, length of disease, gender, underlying etiology, co-diagnosis of Asthma and/or COPD, NTM infection, smoking status, blood eosinophil count and FACED score

%TBE = Total bronchiectasis (%TBE); %TMP = Total mucus plugging; %TinF = Total inflammatory features; %DIS = Total disease.

scores (p <0.01) and a trend for ≥2 admissions (p=0.06). This association can be affected by the timing of the questionnaire assessment, which could lie before or after date of the CT. A univariate sensitivity analysis of this variable in the two groups (CT before vs. CT after questionnaire) did suggest that the association may be driven mostly by the patients in whom the questionnaire was completed before, or up to, the date of the CT (data not shown).

No significant associations were found between smoking history or elevated blood eosinophils and any of the composite BEST-CT outcomes.

Reproducibility

Intra-class correlations coefficients of the BEST-CT method are presented in Supplement S2. For the BEST-CT method, ICC scores within the main observer were all excellent, except for GGO which was poor due to the very low prevalence of detection.

Discussion

Bronchiectasis is a highly heterogeneous disease with a wide variety of etiologies and clinical, microbiological, inflammatory and functional attributes. We used the BEST-CT scoring method to systematically describe the abnormalities on chest CT scans of a diverse cohort of 524 patients in the EMBARC bronchiectasis registry and found large heterogeneity in both the nature and extent of structural lung abnormalities. Notably, the total volume of abnormalities varied greatly, ranging from 5% to nearly 90%. Several clinical characteristics were significantly associated with distinct BEST-CT composite scores.

The two most frequently found lung abnormalities were bronchiectasis without mucus plugging, and mucus plugging. Bronchiectasis is generally viewed as the result of previous long term airway inflammation, leading to irreversible structural damage. The presence of mucus plugging on the other hand is in general evidence of active ongoing inflammation. Indeed, mucus plugging made the largest contribution to the inflammatory composite score %TInf. It is important to note that the scans included in this analysis were performed during diagnosis and routine follow-up of stable disease. Mucus plugging can lead to airflow obstruction and impaired lung function, as is also clearly shown in our data. The accumulation of mucus in the airways is an important part of the vicious cycle, increasing the susceptibility to more infections, exacerbations, and further progression of structural lung damage. Importantly, mucus plugs that occlude large to medium size airways have been independently associated

to lung function and even mortality in COPD, which is another entity in the muco-obstructive lung diseases [18]. The significant association we observed between %TInf, especially, and the number of exacerbations defined by hospital admission, supports the notion that this subgroup of bronchiectasis patients exhibits a higher level of disease activity and possible clinical sequelae [19]. Thus, the radiologic phenotype of bronchiectasis could help identify these patients and may have consequences for clinical care. Addressing mucus clearance is considered a crucial part of current bronchiectasis management plans [20, 21]. While previous studies have indeed suggested the crucial role of inflammation in bronchiectasis, the radiological evidence of mucus plugging in this large cohort of stable bronchiectasis patients, as presented in this study, adds substantial support to this viewpoint [22].

Our study further highlights the significance of infection as crucial component of the pathophysiology of bronchiectasis. Patients with a PsA isolation had more bronchiectasis as well as evidence of a greater degree of small-airways disease, indicated by more mucus plugging.

These findings align with previous studies that have demonstrated a correlation between PsA colonization in patients with bronchiectasis and an increased risk of exacerbations, and more pronounced structural lung abnormalities observed on CT scans [12, 13, 23, 24].

Patients who had a confirmed active NTM infection exhibited even more pronounced lung abnormalities on CT scans, with average differences between patients with or without an NTM infection about 2 to 3 times higher compared to patients with or without a PsA infection. And while PsA was not significantly associated with total inflammatory features, NTM was clearly and significantly associated. These findings corroborate previous research published by Faverio et al. [25], which also demonstrated that active NTM infections are associated with a greater burden of structural lung abnormalities compared to PsA. Interestingly, they did not find these structural abnormalities to be associated with increased disease severity and exacerbations, which contrasts with the trends indicated by our data. The presence of more bronchial wall thickening and bronchiectasis without mucus plugging indicates chronic inflammation and actual remodeling of the bronchial walls, implying a more severe and chronic disease process in patients with NTM. Overall, our findings provide additional evidence that NTM isolates in patients with bronchiectasis are associated with the more severe spectrum of the disease, with evidence of both chronic structural lung abnormalities and active ongoing inflammation, promoting the importance of considering the specific microbial status when assessing disease severity and progression.

An essential part in the diagnostic work-up and management of patients with bronchiectasis is the identification of the underlying etiology and comorbidities [26-28]. An important finding of our study is the fact that different underlying etiologies were found to associate with some but not all BEST-CT composite scores.

Interestingly, patients with PCD, as cause of bronchiectasis, had significantly more mucus plugging and total inflammatory features. This finding is in agreement with a small observational study of Rademacher et al, which also showed that PCD patients tend to have more atelectasis, mucus plugging and a tree-in-bud pattern [29]. These findings may be relevant for the selection of patients for more intensive mucus clearance, anti-inflammatory and/or antibiotic strategies. In contrast to the participants with more signs of active inflammation, those participants with post-infectious etiology and also ABPA had no significant association with total mucus plugging or inflammatory scores. This supports the concept of a subgroup of patients with established bronchiectasis due to a historic episode with infection and inflammation, but with no active ongoing inflammatory disease in the airways. Again, these findings could be important to recognize a phenotype of more stable bronchiectasis patients who could in theory be managed safely with a less intensive treatment strategy. This is the first study that highlights the potential of CT imaging to identify specific radiologic phenotypes, which could possibly be used to improve personalized treatment plans.

The finding that co-diagnosis of asthma and/or COPD relates with a significantly lower extent of bronchiectasis is important in light of research on bronchiectasis and COPD and/or asthma overlap syndromes [30-32]. A lower %TBE suggests that the symptoms of these patients could arise predominantly from their small airways disease rather than the middle to larger airways where bronchiectasis is typically detected. The increased use of high resolution CT may reveal previously unnoticed bronchiectasis in asthma or COPD patients, which have then been included as a subgroup with milder radiological abnormalities in the EMBARC registry [33]. Whether these patients have indeed less relevant bronchiectasis and a different response to treatment remains to be determined. [32, 34]. In a cohort of Czech COPD patients, up to 30.5% were found to have bronchiectasis-COPD overlap syndrome, while a large subgroup of those did not have typical bronchiectasis symptoms [35]. Our data did not show any evidence of a difference of this association between males and females. Finally, it can be appreciated that COPD and also immunodeficiencies (primary and secondary) were in fact associated with less structural abnormalities, most notably significantly less total bronchiectasis.

Our study has several limitations. First, our study is cross-sectional and so does not allow for causal conclusions. Secondly, the selection of participating centres from the

EMBARC network might not be fully representative of all European bronchiectasis patients. Though patient selection within centres was random, minimizing selection bias, the retrospective collection of CT performed with non-standardized scan protocols, non-lung volume controlled scanning and different scanner models could lead to misclassification of CT scores. Any inconsistencies in scan quality, however, are likely non-differential, suggesting our reported associations might be understated. A further limitation is the median time interval of approximate 7 months between the CT scans and enrollment in the EMBARC registry, meaning scans might not align precisely with clinical data timing. This is of particular importance when interpreting the association with clinical characteristics that can vary over time, particularly hospital admissions in the last year and FEV1. Indeed, the association between number of admissions and CT outcomes did appear to be stronger in those with assessment of clinical data before or up to date of CT. Although this could suggest that recurrent exacerbations precede the structural lung changes rather than the other way around, we do not have the statistical power nor the required longitudinal data to substantiate this claim. Notably, 4% of study participants did not show bronchiectasis via the BEST-CT score. These patients still can have subtle bronchiectasis. In the BEST-CT scoring method 10 random but evenly spaced chest-CT slices between lung apex and base are assessed, so small areas of bronchiectasis outside of these 10 slices may have been missed. It should however also be noted that scoring of bronchiectasis relies on visual and thus somewhat subjective estimation by observers. A cutoff ratio between airway and artery diameter of 1.5 or higher is generally recommended for airway widening, and visual estimation is even less sensitive to milder signs of airway wall thickening. Future research might use automated, artificial intelligence-driven scoring for accuracy. CT scans annotated as part of this project can aid in developing such automated algorithms using artificial intelligence.

Another limitation is the combination of atelectasis and consolidation as one anomaly. It is known that these are two different CT characteristics. Since this was a retrospective study, not all patients were scanned with contrast, making it sometimes challenging to distinguish between these two CT features. Finally, it should be noted that as we investigated the associations between a range of possible predictor variables and structural lung outcomes, there is a chance of risk findings due to multiple testing. No formal correction for multiple testing was performed, which needs to be taken into account in the interpretation of our results.

This study is one of the largest to systematically study the relationship between a variety of radiological abnormalities and clinical phenotypes in a cohort of bronchiectasis patients [36]. Historically, improved methods to classify and quantify radiological abnormalities, like bone fractures and vascular lesions have deepened our understanding of the links between the disease, etiological factors and patient subgroups [37, 38]. For

bronchiectasis, developing objective ways to categorize and measure radiological lung changes can advance our understanding of inflammation and infection mechanisms, lung function impairment, disease progression monitoring, and therapy customization. In this study, we have shown associations between radiological manifestations and patient factors, increasing our understanding of the disease mechanisms in different patient subgroups. Moreover, we have demonstrated the value of a radiological scoring method in a large cohort of patients to demonstrate such associations. In the future, adoption of fully automated scoring systems may further facilitate these investigations. Automated assessment of all bronchi and accompanying arteries has been shown to be sensitive to detect airway widening and airway wall thickening in cystic fibrosis populations [39, 40], non-CF bronchiectasis [36, 41] and pediatric asthma. Analysis of the EMBARC cohort using automated analysis is ongoing.

In summary, we conclude that structural lung abnormalities in bronchiectasis patients is heterogeneous and extensive with prominent inflammatory features. Lower FEV1, PsA, NTM, severe exacerbations and bronchiectasis etiology were strongly correlated with the extent of structural lung abnormalities on chest CT scans. The quantitative BEST-CT outcomes can be used to phenotype structural lung abnormalities in bronchiectasis patients and uncover the relationship between patient characteristics and radiological disease manifestations.

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References

1. Aliberti, S., 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, 2022. **10**(3): p. 298-306.
2. Flume, P.A., J.D. Chalmers, and K.N. Olivier, *Advances in bronchiectasis: endotyping, genetics, microbiome, and disease heterogeneity.* Lancet, 2018. **392**(10150): p. 880-890.
3. Hansell, D.M., et al., *Fleischner Society: glossary of terms for thoracic imaging.* Radiology, 2008. **246**(3): p. 697-722.
4. Meerburg, J.J., et al., *Diagnosis and quantification of bronchiectasis using computed tomography or magnetic resonance imaging: A systematic review.* Respir Med, 2020. **170**: p. 105954.
5. Meerburg, J.J., et al., *Analysis of Granulomatous Lymphocytic Interstitial Lung Disease Using Two Scoring Systems for Computed Tomography Scans-A Retrospective Cohort Study.* Front Immunol, 2020. **11**: p. 589148.
6. Jennifer J. Meerburg, A.G.-U., Olivier Dragt, Eleni-Rosalina Andrinopoulou, Mariette, P.C. Kemner van de Corput, Pierluigi Ciet, Gerhild Angyalosi, J. Stuart Elborgn, James D. Chalmers, Michael Tunney, Merleen de Bruine, Harm A.W.M. Tiddens, on behalve of the iABC study group, *Quantitative chest computed tomography scoring technique for bronchiectasis (BEST-CT).* Submitted.
7. Meerburg, J., et al., *Novel quantitative bronchiectasis scoring technique for chest computed tomography: BEST-CT. A study within the iABC project.* European Respiratory Journal, 2019. **54**(suppl 63): p. PA4817.
8. Chalmers, J.D., et al., *The EMBARC European Bronchiectasis Registry: protocol for an international observational study.* ERJ Open Res, 2016. **2**(1).
9. Chalmers, J.D., et al., *Bronchiectasis in Europe: data on disease characteristics from the European Bronchiectasis registry (EMBARC).* Lancet Respir Med, 2023. **11**(7): p. 637-649.
10. Griffith, D.E., et al., *An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases.* Am J Respir Crit Care Med, 2007. **175**(4): p. 367-416.
11. Zhou, Y., et al., *Global prevalence of non-tuberculous mycobacteria in adults with non-cystic fibrosis bronchiectasis 2006-2021: a systematic review and meta-analysis.* BMJ Open, 2022. **12**(8): p. e055672.
12. Chalmers, J.D., et al., *The bronchiectasis severity index. An international derivation and validation study.* Am J Respir Crit Care Med, 2014. **189**(5): p. 576-85.
13. Martínez-García, M., et al., *Multidimensional approach to non-cystic fibrosis bronchiectasis: the FACED score.* Eur Respir J, 2014. **43**(5): p. 1357-67.
14. Shoemark, A., et al., *Characterization of Eosinophilic Bronchiectasis: A European Multicohort Study.* Am J Respir Crit Care Med, 2022. **205**(8): p. 894-902.
15. Rosenow, T., et al., *PRAGMA-CF. A Quantitative Structural Lung Disease Computed Tomography Outcome in Young Children with Cystic Fibrosis.* Am J Respir Crit Care Med, 2015. **191**(10): p. 1158-65.
16. Kuo, W., et al., *Objective airway artery dimensions compared to CT scoring methods assessing structural cystic fibrosis lung disease.* J Cyst Fibros, 2017. **16**(1): p. 116-123.
17. Koo, T.K. and M.Y. Li, *A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research.* J Chiropr Med, 2016. **15**(2): p. 155-63.
18. Diaz, A.A., et al., *Airway-Occluding Mucus Plugs and Mortality in Patients With Chronic Obstructive Pulmonary Disease.* Jama, 2023. **329**(21): p. 1832-1839.
19. Mikami, Y., et al., *Chronic airway epithelial hypoxia exacerbates injury in muco-obstructive lung disease through mucus hyperconcentration.* Sci Transl Med, 2023. **15**(699): p. eabo7728.

20. Muñoz, G., et al., *Long-term benefits of airway clearance in bronchiectasis: a randomised placebo-controlled trial.* Eur Respir J, 2018. **51**(1).
21. Herrero-Cortina, B., et al., *European Respiratory Society statement on airway clearance techniques in adults with bronchiectasis.* Eur Respir J, 2023. **62**(1).
22. Keir, H.R., et al., *Neutrophil extracellular traps, disease severity, and antibiotic response in bronchiectasis: an international, observational, multicohort study.* Lancet Respir Med, 2021. **9**(8): p. 873-884.
23. Finch, S., et al., *A Comprehensive Analysis of the Impact of Pseudomonas aeruginosa Colonization on Prognosis in Adult Bronchiectasis.* Ann Am Thorac Soc, 2015. **12**(11): p. 1602-11.
24. Miszkiel, K.A., et al., *Effects of airway infection by Pseudomonas aeruginosa: a computed tomographic study.* Thorax, 1997. **52**(3): p. 260-4.
25. Faverio, P., et al., *Characterizing Non-Tuberculous Mycobacteria Infection in Bronchiectasis.* Int J Mol Sci, 2016. **17**(11).
26. Pasteur, M.C., D. Bilton, and A.T. Hill, *British Thoracic Society guideline for non-CF bronchiectasis.* Thorax, 2010. **65 Suppl 1**: p. i1-58.
27. Hill, A.T., et al., *British Thoracic Society guideline for bronchiectasis in adults.* BMJ Open Respir Res, 2018. **5**(1): p. e000348.
28. Polverino, E., et al., *European Respiratory Society guidelines for the management of adult bronchiectasis.* European Respiratory Journal, 2017. **50**(3): p. 1700629.
29. Rademacher, J., et al., *The Primary Ciliary Dyskinesia Computed Tomography Score in Adults with Bronchiectasis: A Derivation und Validation Study.* Respiration, 2021. **100**(6): p. 499-509.
30. Hurst, J.R., J.S. Elborn, and A. De Soyza, *COPD-bronchiectasis overlap syndrome.* Eur Respir J, 2015. **45**(2): p. 310-3.
31. Jin, J., et al., *Factors associated with bronchiectasis in patients with moderate-severe chronic obstructive pulmonary disease.* Medicine (Baltimore), 2016. **95**(29): p. e4219.
32. Zhang, X., et al., *Risk factors for bronchiectasis in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis.* Clinics (Sao Paulo), 2021. **76**: p. e2420.
33. van den Bosch, W.B., A.L. James, and H. Tiddens, *Structure and function of small airways in asthma patients revisited.* Eur Respir Rev, 2021. **30**(159).
34. Magis-Escurra, C. and M.H. Reijers, *Bronchiectasis.* BMJ Clin Evid, 2015. **2015**.
35. Brat, K., et al., *The Relation Between Clinical Phenotypes, GOLD Groups/Stages and Mortality in COPD Patients - A Prospective Multicenter Study.* Int J Chron Obstruct Pulmon Dis, 2021. **16**: p. 1171-1182.
36. Aliboni, L., et al., *Detection and Classification of Bronchiectasis Through Convolutional Neural Networks.* J Thorac Imaging, 2022. **37**(2): p. 100-108.
37. Kuo, R.Y.L., et al., *Artificial Intelligence in Fracture Detection: A Systematic Review and Meta-Analysis.* Radiology, 2022. **304**(1): p. 50-62.
38. van Leeuwen, K.G., et al., *How does artificial intelligence in radiology improve efficiency and health outcomes?* Pediatr Radiol, 2022. **52**(11): p. 2087-2093.
39. Chen, Y., et al., *Automatic bronchus and artery analysis on chest computed tomography to evaluate the effect of inhaled hypertonic saline in children aged 3-6 years with cystic fibrosis in a randomized clinical trial.* J Cyst Fibros, 2023. **22**(5): p. 916-925.
40. Lv, Q., et al., *Automatic analysis of bronchus-artery dimensions to diagnose and monitor airways disease in cystic fibrosis.* Thorax, 2023. **79**(1): p. 13-22.
41. al, P.e., *Automatic analysis of bronchus and artery dimensions of an adult bronchiectasis population.* Submitted.

Supplemental Tables/Figures

Table E1. Intraclass correlation coefficients of BEST-CT scoring method

Scores	Intra	Inter
%ATCON	0.98	0.93
%BEMP	0.99	0.29
%BEwMP	0.99	0.75
%TBE	0.99	0.93
%AWT	0.95	0.69
%MP	0.91	0.63
%GGO	0.19	0.60
%BUL	0.99	0.99
%HA	0.89	0.30
%HP	0.97	0.83

This table presents intra- and inter-observer agreement for the BronchiEctasis Scoring Technique for Computed Tomography (BEST-CT) expressed in intra-class correlation coefficients (ICC). ATCON = Atelectasis and/or consolidation; BEMP = Bronchiectasis with mucus plugging. BEwMP = Bronchiectasis without mucus plugging; TBE = total bronchiectasis (BEMP + BEwMP). AWT = airway wall thickening. MP = Mucus plugging; GGO = Ground-glass opacities. BUL = bullae. A = airways. P = parenchyma.

Chapter 3

Automated Method of Bronchus and Artery Dimension Measurement in an Adult Bronchiectasis Population

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Abstract

Aim: Bronchiectasis (BE) is a disease defined by irreversible dilatation of the airway. Computed tomography (CT) plays an important role in the detection and quantification of BE. The aim of this study was three-fold: 1) to assess bronchus-artery (BA) dimensions using fully automated software in a cohort of BE disease patients; 2) to compare BA dimensions with semi-quantitative BEST-CT (Bronchiectasis Scoring Technique for CT) scores for BE and bronchial wall thickening; and 3) to explore the structure-function relationship between BA-method lumen dimensions and spirometry outcomes.

Methods: Baseline CTs of BE patients who participated in a clinical trial were collected retrospectively. CTs were analysed manually with the BEST-CT scoring system and automatically using LungQ (v.2.1.0.1, Thirona, The Netherlands), which measures the following BA dimensions: diameters of bronchial outer wall (B_{out}), bronchial inner wall (B_{in}) and artery (A), and bronchial wall thickness (B_{wt}) and computes BA ratios (B_{out}/A and B_{in}/A) to assess bronchial widening. To assess bronchial wall thickness, we used the B_{wt}/A ratio and the ratio between the bronchus wall area (B_{wa}) and the area defined by the outer airway (B_{oa}) (B_{wa}/B_{oa}).

Results: In total, 65 patients and 16 900 BA pairs were analysed by the automated BA method. The median (range) percentage of BA pairs defined as widened was 69 (55-84)% per CT using a cut-off value of 1.5 for B_{out}/A, and 53 (42-65)% of bronchial wall were thickened using a cut-off value of 0.14 for B_{wt}/A. BA dimensions were correlated with comparable outcomes for the BEST-CT scoring method with a correlation coefficient varying between 0.21 to 0.51. The major CT BA determinants of airflow obstruction were bronchial wall thickness (p=0.001) and a narrower bronchial inner diameter (p=0.003).

Conclusion: The automated BA method, which is an accurate and sensitive tool, demonstrates a stronger correlation between visual and automated assessment and lung function when using a higher cut-off value to define bronchiectasis.

Introduction

Bronchiectasis in adults is a common complication of a wide array of respiratory diseases and is characterized by airway widening, and clinical symptoms. Clinical symptoms can consist of cough, sputum production, recurrent chest infections, malaise, chest discomfort and in severe cases hemoptysis and weight loss [1]. The presence of bronchiectasis can be suspected based on clinical symptoms, auscultatory abnormalities, and on lung function impairment. Unfortunately, these indicators lack sensitivity and specificity. Patients diagnosed with bronchiectasis have airflow obstruction on spirometry in around 50% of cases, but restrictive or mixed obstructive patterns and preserved lung function are also frequently observed [2, 3]. For the objective and sensitive diagnosis of bronchiectasis chest computed tomography (CT) is considered the gold standard. The most widely accepted definition of bronchiectasis by radiologists as observed on chest CT is a dilatation of the airway that is larger compared to the adjacent artery, lack of tapering, and visibility of an airway in the periphery of the lung [4-6]. However, these criteria are subjective, and it is unclear to what extent these criteria are correctly applied in clinical practice, clinical trials and research studies [4, 7]. In addition, chest CT image acquisition is poorly standardized which can affect the diagnosis of bronchiectasis [5, 8, 9].

For these reasons, there is great need for objective reproducible quantitative radiological methods to assess the presence and extend of bronchiectasis [4]. Therefore, the Bronchiectasis Scoring Technique for CT (BEST-CT) was developed based upon a validated scoring method to quantify structural lung damage in patients with cystic fibrosis (PRAGMA-CF) [10]. BEST-CT was shown to be a reproducible quantitative scoring system to phenotype and measure the severity and extent of the structural lung abnormalities in bronchiectasis patients [11]. Disadvantages of the BEST-CT system are that it requires a one to two weeks training of the observer, and that it is time consuming taking up to 45 minutes to score one CT scan. Furthermore, the scoring is still based on eye-balling by the observer to estimate airway, artery and airway wall dimensions and ratios for the diagnosis of bronchiectasis and airway wall thickening.

Recently, a fully automated image analysis system was developed using artificial intelligence (AI) strategies that allows to measure with great accuracy and precision the dimensions of a large number of bronchus-artery (BA) pairs on a chest CT scan. To date, this automated BA-method has been used to assess BA-dimensions in various CF cohorts, in a severe asthma cohort, and in a large set of normal chests CTs [12, 13].

The aim of the current study was three-fold: (1) to assess BA-dimensions using the fully automated BA-method in a cohort of bronchiectasis patients that participated in

a phase-2 clinical trial [11]; (2) to compare BA-outcomes dimensions with the semi-quantitative BEST-CT scores for bronchial widening and bronchial wall thickening; (3) to explore the structure function relationship between BA-method bronchial wall and lumen dimensions and spirometry outcomes.

We hypothesized that the automated BA-method is an accurate and sensitive tool to assess airways disease in bronchiectasis patients and that its output correlates with the BEST-CT scoring system and spirometry outcomes.

Materials and methods

Study population

The CTs for the study were retrospectively collected from bronchiectasis patients who participated in the iBEST study [14]. The iBEST study was a randomized placebo controlled trial designed to evaluate the efficacy, safety and tolerability of tobramycin inhalation powder in bronchiectasis patients. Inclusion criteria for the study were patients (aged ≥18 years) with a proven diagnosis of bronchiectasis confirmed on the CT scan by the local radiologists and a history of ≥2 exacerbations treated with oral antibiotics or ≥1 exacerbation treated with parenteral antibiotic treatment as well as a respiratory sputum sample positive for *Pseudomonas aeruginosa*. Main exclusion criteria were diagnosis of CF, primary diagnosis of bronchial asthma, and smoking-associated chronic obstructive pulmonary disease (COPD). Other inclusion and exclusion criteria are detailed in the study design manuscript [15].

All CTs, which were baseline scans made prior to the trial, were previously analyzed using the BEST-CT scoring system before treatment [16]. Inclusion criteria for the automated BA-method was the availability of an inspiratory CT scan with a reconstructed slice thickness of axial images of ≤ 1.5 millimeter (mm), no missing lung, and no gaps between slices.

For all patients included in this sub-study the following spirometry outcomes were available and expressed as % predicted using the Global Lung Initiative prediction equations[17]: forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and forced expiratory flow between 25 and 75% of vital capacity ($FEF_{25-75\%}$).

BEST-CT scoring

BEST-CT is a morphometric scoring system for which a grid is placed on 10 equally spaced axial chest-CT slices between lung apex and base. Each grid box is annotated by an observer for the presence or absence of structural lung abnormalities [11]. Each

grid cell that contains at least 50% coverage of the lung is scored. The structure in the grid cell is scored with the following hierarchical system (highest to lowest priority): 1. Atelectasis/consolidation (ATCON), 2. bronchiectasis with mucous plugging (BEMP), 3. bronchiectasis without mucous plugging (BEwMP), 4. Airway wall thickening (AWT), 5. Mucous plugging without bronchiectasis (MP), 6 ground-glass opacities (GGO), 7. Emphysema and/or bullae (EMPBUL), 8. Healthy airways (HA) and 9. Healthy parenchyma (HP). Bronchiectasis was considered by the observer when the outer wall of an airway was estimated to be wider than the adjacent artery and airway wall thickening when the internal diameter of the bronchus was <80% of the external diameter.

The total percentage of lung volume occupied by bronchiectasis and airway wall thickening for BEST-CT are calculated in the following composite score which are used for comparison with similar automated BA-method outcomes: %BE_BESTCT = %BEMP + %BEwMP and %AWT_BESTCT = %AWT.

Bronchus-Artery analysis

The automated BA-method was performed using LungQ version 2.1.0.1 (Thirona, Nijmegen, The Netherlands, https://www.thirona.eu). The term bronchus and its abbreviation (B) was selected over airway and its abbreviation (A) to avoid confusion with abbreviation of artery (A). LungQ is an AI-based medical image analysis platform that amongst others automatically identifies patient-specific anatomical features, and structural bronchial and parenchymal abnormalities on chest CT scans.

The AI-based algorithms of LungQ are trained with a large variety of datasets to ensure robust performance against variation in patient characteristics (age, gender, BMI), disease populations (COPD, asthma, CF, interstitial lung disease, chronic bronchitis, bronchiectasis, COVID-19) and variation in image characteristics (manufacturer, dose, convolutional kernel, voxel spacing). To ensure a robust performance in patients with bronchiectasis, an additional training was performed on around 1.5 million training samples (including data augmentation techniques) from BA matches in CT scans of bronchiectasis patients.

The automated BA-method starts by automatically detecting and segmenting the bronchial tree on an inspiratory CT scan. Next, for each bronchus starting at the segmental bronchus (G_0) and for higher generations ($G_{1\text{-}14}$) the adjacent artery is identified using an AI-based BA matching algorithm. Next, for each identified BA-pair and segmental bronchus generation the following dimensions are computed perpendicular to the longitudinal bronchus or artery axis (figure 1): Bronchial inner diameter (B_{in}); Bronchial outer diameter (B_{out}); Bronchial wall thickness (B_{wt} (=(B_{out}-

B_{in})/2)), bronchial wall area (B_{wa}), bronchial outer area (B_{oa}) and Artery diameter (A). The bronchi quantification utilizes a proprietary intensity profile quantification algorithm that allows for sub-resolution quantification for bronchial wall thickness. The algorithm quantifies each individual bronchus cross-section perpendicular to the local bronchial direction by calculating the bronchial dimensions in a multitude of radial intensity profiles with a sampling distance of higher resolution than the resolution of the scan. For each bronchial generation G_0 and higher, the BA-dimensions of each individual bronchial branch is computed as the average of all measurements within that branch.

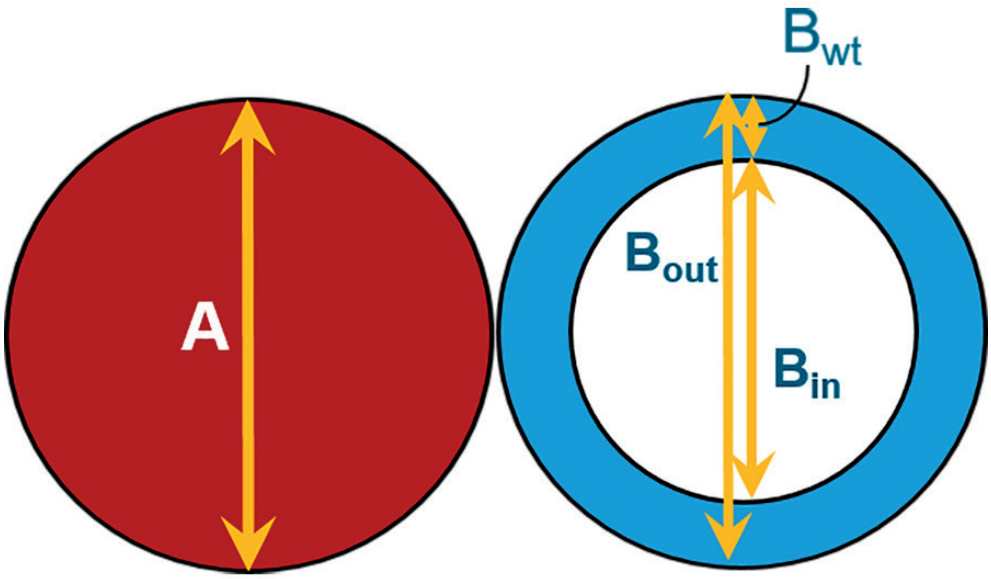

Figure 1. **Bronchial Artery (BA)-ratio**.

This figure shows an example of the dimensions measured on a chest CT for each BA-pair as measured by the automatic BA-method software (Thirona B.V., The Netherlands). B_{out}: Bronchial outer diameter; B_{in}: bronchial inner diameter; B_{wt}: Bronchial wall thickness; A: the adjacent artery diameter.

The following ratios for each BA-pair is calculated by LungQ:

- B_{out}/A: the ratio between bronchial outer diameter and adjacent artery diameter;
- B_{in}/A: the ratio between bronchial inner diameter and adjacent artery diameter;
- B_{wt}/A: the ratio between bronchial wall thickness and adjacent artery diameter.
- B_{wa}/B_{oa} = the ratio between bronchial wall area and bronchial outer area.

In addition, we computed the P_{i10} which is the square root of the wall area for a hypothetical airway with an internal perimeter of 10 mm, obtained by projecting the set of extracted dimensions using linear regression [18, 19]. The P_{i10} has been used as an indicator for bronchial wall thickness in adult smokers but it does not take body size nor generation into account and it can be influenced by a reduced internal diameter in relation to mucus. For this reason, we also used B_{wt}/A ratio and the ratio between the wall area (B_{wa}) and the area defined by the outer airway (B_{oa}) (B_{wa}/B_{oa}) to assess bronchial wall thickness.

For each patient bronchial dimensions and ratios are computed and plotted against segmental generation (G_0 and higher), since airways of the same generation have similar sizes and characteristics.

The cut-off values to determine bronchial widening and bronchial wall thickening are based on the automated BA-method of a previously manual annotated dataset of chest CTs from patients with CF and from normal CTs of age matched control subjects [20]. As there is no universally accepted definition for bronchial widening [5], we use a cut off value for B_{out}/A of ≥ 1.1 based the automated BA-method of a previous data set [12] and a more conservative cut off value of ≥ 1.5 [7] as suggested in a consensus publication based on a Delphi process by an international taskforce of experts to develop recommendations and definitions for bronchiectasis. Furthermore, we use cut off values for B_{in}/A-ratio for bronchial widening of ≥ 0.8 and ≥1.5. Bronchial wall thickening was defined as B_{wt}/A-ratio ≥0.14 and assessed using the median of B_{wa}/B_{oa}. Total lung volume was assessed by LungQ.

Statistical analysis

BA-dimensions results are presented from sub-segmental level onward ($G_{1\text{-}14}$), where G_1 represents the sub-segmental bronchi, G_2 the sub-sub-segmental bronchi and so on. For statistical analysis, we use the median values of BA-dimensions and ratios of $G_{1\text{-}6}$ as these generations include the highest number of BA-measurements in most patients and is less affected by body size and by higher visibility of small airways in relation to airways disease. To investigate whether the differences between BEST-CT outcomes with the automated BA-method and their relation with clinical parameters were depended on our selected segmental generations ($G_{1\text{-}6}$), we executed a sensitivity analysis to determine the optimal number of segmental generations to be included ($G_{1\text{-}6}$ or $G_{1\text{-}14}$) in our analysis.

Data are shown as median and interquartile range (IQR) (25^{th} -75^{th} percentile) or as mean ± standard deviation depending on the data distribution.

BEST-CT versus BA-dimensions:
For the comparison between BEST-CT results (%BE_BESTCT and %BWT_BESTCT) and comparable BA-dimensions (B_{out}/A, B_{in}/A and B_{wt}/A ratios) we used Spearman correlation coefficients because of the skewed data distribution. A correlation coefficient lower than 0.2 was rated as very weak, 0.2-0.4 as weak, 0.4-0.6 as moderate, 0.6-0.8 as strong, and 0.8-1 as excellent[21].

Spirometry versus automated BA-method
For the comparison between BA-dimensions related to airway obstruction ($B_{in,}$ B_{wt}, B_{out}/A, B_{in}/A, B_{wa}/B_{oa} and P_{i10} for G_{1-6}) and spirometry outcomes sensitive to airway obstruction (FEV_1% predicted, FEV_1/FVC% predicted and log $FEF_{25-75\%}$ %predicted) we used linear regression analysis. For the BA-method B_{in} was selected as the most relevant outcome measure as the internal diameter of the airways is the most likely outcome measure determining maximal flows for a spirometry maneuver. For the spirometry outcomes FEV_1% predicted, FEV_1/FVC% predicted and log $FEF_{25-75\%}$ predicted were selected as these outcomes are considered dependent on the bronchial lumen dimensions. Correlations between B_{in}, B_{wt}, B_{out}/A, B_{in}/A B_{wa}/B_{oa}, and P_{i10} and FEV_1, FEV_1/FVC, and $FEF_{25-75\%}$ were assessed by Spearman (or Pearson) correlation coefficients depending on whether the data had skewed distribution. We used a logarithmic scale for $FEF_{25-75\%}$ since the data distribution is skewed.

Adjusted p-values were used for multiple testing in relation to comparison between the BA-dimensions and spirometry outcomes.

All statistical analysis was done using R tooling, version 4.0.5 (R Foundation for Statistical Computing. Vienna, 2005). Statistically significant results were defined as a p-value less than 0.05.

Results

CT Collection and study population

84 inspiratory scans were analyzed using the BEST-CT method and of these scans 69 were eligible for automated BA-method using LungQ software. 15 scans could not be included in the analyses due to slice thickness above 1.5 mm and/or inconsistency in slice spacing. Patient characteristics are present in table 1.

Table 1. Patient characteristics and results of CT-analysis by the automatic BA-method

	iBEST-CT dataset
Age (Years) - Median [IQR]	65 [58 – 74]
Gender (Male/Female) - number (%)	24 (34.5)/ 45 (65.5)
Spirometry – Median [IQR]	
FEV_1, %pred	58.1 [45.9 - 71.0]
FVC, %pred	72.3 [64.4- 89.4]
FEV_1/FVC, %pred	72.3 [64.4 - 89.4]
$FEF_{25-75\%}$, %pred	30.3 [21.0 - 42.4]
Number of analyzed CT scans	69
Total number of bronchi	24,190
Bronchi count per CT	319 [228, 441]
Total number of BA-pairs	16,900
BA-pair count per CT	235 [165-344]
Percentage of abnormal BA-pairs Median [IQR]	
B_{out}/A cut-off of ≥ 1.1	68.5 [54.9 - 84.3]
B_{out}/A cut-off of ≥1.5	34.8 [23.0 - 43.6]
B_{in}/A cut-off of ≥0.8	74.9 [57.3 - 86.2]
B_{in}/A cut-off of ≥1.5	7.6 [3.3 - 15.9]
B_{wt}/A cut-off of ≥0.14	53.4 [42.0 - 65.4]

Chest CT-related characteristics. Inspiratory scans were analyzed by the automatic BA-method. Bronchial widening were defined as B_{out}/A-ratio cut-off of ≥ 1.1 and ≥1.5 and B_{in}/A-ratio cut-off of ≥ 0.8 and ≥1.5. Bronchial wall thickening was defined as B_{wt}/A-ratio cut-off of ≥ 0.14. Data are mean±SD or median [IQR].

BA = bronchus and artery pair. B_{in}/A= bronchial inner diameter divided by adjacent artery diameter. B_{out}/A= bronchial outer dimeter divided by adjacent artery diameter. B_{wt}/A= bronchial wall thickness divided by adjacent artery diameter. $FEV_{1,}$ %pred= forced expiratory volume in 1 second as a percentage of predicted forced expiratory volume in 1 second; FVC= forced vital capacity as a percentage of predicted forced vital capacity; $FEF_{25-75\%}$= forced expiratory flow between 25 and 75% of vital capacity as a percentage of predicted forced expiratory flow. CT= computed tomography; SD=standard deviation; BA=bronchus-artery; IQR=interquartile range.

Automated analysis

A total number of 24,190 bronchi and 16,900 BA pairs were analyzed by the automated BA-method ranging from segmental generations G_0 up to G_{14}. The median [IQR] of airway count per CT was 319 [228- 441] and the median [IQR] of BA-pair count per CT was 235 [165-344]. The median percentage per CT of BA-pairs defined as bronchial widening was 69% and 35% using an B_{out}/A-ratio cut-off of ≥ 1.1 and ≥ 1.5, respectively (table 1) (Supplementary material, Figure 1&2). The median percentage per CT of BA-pairs defined as bronchial widening was 75% and 8% using an B_{in}/A-ratio cutoff off ≥ 0.8 and ≥ 1.5 (table 1) (Supplementary material, Figure 1&2). The

median percentage per CT of BA-pairs showing bronchial wall thickening was 53% for B_{wt}/A cut-off of ≥ 0.14 (Table 1) (Supplementary material, Figure 1&2).

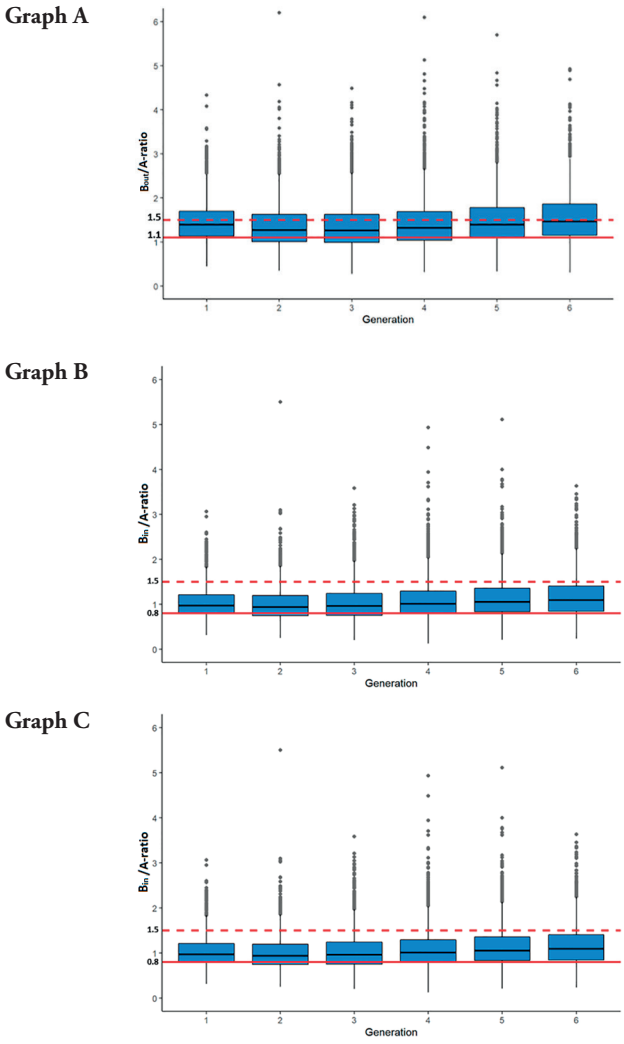

Figure 2. Bronchial-artery ratio's

This figure shows the B_{out}/A, B_{in}/A and B_{wt}/A-ratio's starting at the segmental level (generation 0) for generation 1 to 6. The gray dots indicate individual bronchus-artery ratios. The blue boxes indicate the median and interquartile range (25^{th}-75^{th} percentile). **Graph A** shows the B_{out}/A-ratio. The bold red line indicates the B_{out}/A cut-off of ≥1.1 and the red dotted line the cut-off of ≥1.5 for bronchial widening. **Graph B** shows the B_{in}/A-ratio. The bold red line indicates the B_{in}/A-ratio cut-off of ≥ 0.8 and the red dotted line the cut-off of ≥ 1.5. **Graph C** shows B_{wt}/A-ratio. The bold red line indicates the B_{wt}/A cut-off of 0.14.

For the sensitivity analysis comparing G_{1-6} with G_{1-14} we did not find any significant differences in outcomes for BA-dimensions versus BEST-CT analysis nor for the associations between BA-dimensions and spirometry (Supplementary Material; S1-S5).

Automated BA-method versus BEST-CT analysis

We observed weak to moderate correlations between automated BA-method and BEST-CT outcomes (Table 2). The correlations for the low cut-off values for bronchial widening B_{out}/A cut-off of ≥1.1 and B_{in}/A cut-off of ≥ 0.8) were poor, while for the more conservative cut-off for bronchial widening (B_{out}/A cut-off and B_{in}/A cut-off of ≥1.5 were moderate. For bronchial wall thickness, there was a poor positive correlation between B_{wt}/A-ratio and %BWT_BEST-CT (Table 2).

Table 2. Correlation between BEST-CT and automatic BA-method

	Automatic BA-method for bronchial widening			
	B_{out}/A≥1.1	**B_{out}/A≥1.5**	**B_{in}/A≥0.8**	**B_{in}/A≥1.5**
%BE_BEST-CT	R=0.30 [0.05, 0.53]	R=0.51 [0.29, 0.69]	R=0.21 [-0.05, 0.44]	R=0.46 [0.24, 0.64]
	Automatic BA method for bronchial wall thickening			
	B_{wt}/A≥0.14			
%BWT_BEST-CT	R=0.26 [0.034, 0.47]			

This table shows the correlation between BronchiEctasis Scoring Technique (BEST-CT) outcomes (%BE, %BWT) and automatic BA-method ratios by automatic BA-method (B_{out}/A, B_{in}/A and B_{wt}/A) in generations (G_{1-6}). Bronchial widening was defined as B_{out}/A-ratio ≥ cut-off of 1.1 and ≥1.5 and B_{in}/A ≥ cut-off of 0.8 and 1.5. Bronchial wall thickening was defined as B_{wt}/A-ratio ≥ cut-off of 0.14. This table shows Pearson correlation coefficients (r) and [95% confidence interval].

BA=bronchus-artery; B_{in}/A= bronchial inner dimeter divided by adjacent artery diameter. B_{out}/A= bronchial outer dimeter divided by adjacent artery diameter. B_{wt}/A= bronchial wall thickness divided by adjacent artery diameter;

Associations between automated BA-method and spirometry

We observed positive weak correlations between spirometry parameters (FEV_1% predicted, FEV_1/FVC %predicted and $FEF_{25-75\%}$ %predicted) and the median of B_{in} (G_{1-6}) (Table 3). Regression analysis showed that spirometry parameters correlated significantly to B_{in} (G_{1-6}) (Table 4).

We found significant correlations between spirometry parameters (FEV_1% predicted, FEV_1/FVC% predicted and $FEF_{25-75\%}$ %predicted) and the median of B_{wt} (G_{1-6}) (Table 5). Similar p-values were observed for the P_{i10} and B_{wa}/B_{oa} as a measure for bronchial wall thickening (Table 5). Higher B_{wt} (G_{1-6}), higher P_{i10} and higher B_{wa}/B_{oa} were associated with a lower FEV_1% predicted, FEV_1/FVC% predicted and $FEF_{25-75\%}$

%predicted However, we did not find any significant correlations between spirometry parameters and BA-ratios (B_{in}/A, B_{out}/A and B_{wt}/A) (Supplementary Material; S1-S5).

Table 3. Correlation between spirometry parameters and bronchial inner diameter (Bin,) derived from automated bronchus–artery (BA) method

Spirometry	Median of B_{in}
FEV_1, %pred	R=0.27 [0.04, 0.48]
FEV_1/FVC, %pred	R=0.27 [0.03, 0.48]
$FEF_{25-75\%}$, %pred	R=0.23 [-0.01, 0.45]

This table shows the correlation between spirometry outcomes and the median of bronchial inner diameter (B_{in}) derived from automatic BA-method in limited generations (G_{1-6}). Note that all the results are shown as Spearman (or Pearson) correlation coefficient (r) and [95% confidence interval].

$FEV_{1,}$ %pred = forced expiratory volume in 1 second as a percentage of predicted forced expiratory volume in 1 second; FVC = forced vital capacity as a percentage of predicted forced vital capacity; $FEF_{25-75\%}$ = forced expiratory flow between 25 and 75% of vital capacity as a percentage of predicted forced expiratory flow.

Table 4. Results of linear regression analysis: investigating the association between spirometry parameters and and bronchial inner diameter(Bin,) derived from automated bronchus–artery (BA) method

Spirometry	**Median of B_{in}**	
	Estimates (SE)	**P-value**
FEV_1, %pred	18.84 (7.62)	0.02*
FEV_1/FVC, %pred	14.34 (4.66)	<0.01*
Log ($FEF_{25-75\%}$, %pred)	17.01 (9.03)	0.07

This table shows the regression analysis for spirometry (FEV_1% predicted, FVC% predicted, FEV_1/FVC and log $FEF_{25-75\%}$ predicted) versus the median of B_{in}.

The significant p-value is indicated by *. $FEV_{1,}$ %pred = forced expiratory volume in 1 second as a percentage of predicted forced expiratory volume; FVC = forced vital capacity as a percentage of predicted forced vital capacity; $FEF_{25-75\%}$ = forced expiratory flow between 25 and 75% of vital capacity as a percentage of predicted forced expiratory flow.

Table 5. Results of linear regression analysis: investigating the association between spirometry parameters and bronchial wall thickening by the automated bronchus–artery (BA) method

Spirometry	*Automatic BA-method*					
	Median of B_{wt}/A		**P_{i10}**		**Median of B_{wa}/B_{oa}**	
	Estimates (SE)	**P-value**	Estimates (SE)	**P-value**	Estimates (SE)	**P-value**
FEV_1, %pred	-67.12 (27.83)	0.08	-22.65 (5.71)	<0.01*	-103.15 (28.64)	<0.01*
FEV_1/FVC, %pred	-64.54 (16.22)	<0.01*	-14.55 (3.57)	<0.01*	-71.26 (17.58)	<0.01*
Log ($FEF_{25-75\%}$, %pred)	-1.97 (0.77)	0.08	-0.50 (0.17)	0.03*	-2.33 (0.84)	0.05*

This table shows the regression analysis for spirometry (FEV_1% predicted, FVC% predicted, FEV_1/FVC and log $FEF_{25-75\%}$ predicted) versus the median of bronchial wall thickening described as B_{wt}/A, P_{i10} and B_{wa}/B_{oa}. B_{wt}/A is defined as bronchial wall thickness divided by adjacent artery diameter; P_{i10} is defined as the square root of the wall area for a hypothetical airway with an internal perimeter of 10 mm. B_{wa}/B_{oa} is defined as the ratio between the wall area B_{wa} and the area defined by the outer airway (B_{oa}) (B_{wa}/B_{oa}).

A significant p-value is indicated by *. FEV_1, %pred = forced expiratory volume in 1 second as a percentage of predicted forced expiratory volume in 1 second; FVC = forced vital capacity as a percentage of predicted forced vital capacity; $FEF_{25-75\%}$ = forced expiratory flow between 25 and 75% of vital capacity as a percentage of predicted forced expiratory flow.

Discussion

Using the automated BA-method we were able to detect and quantify a large number of bronchi and BA-pairs to obtain BA-dimensions on chest CT scans in a cohort of bronchiectasis patients participating in a clinical trial. We showed that the BA-dimensions for bronchial widening correlated to comparable outcomes for the BEST-CT scoring method and that airway wall thickness and a wider bronchial lumen diameter as assessed by the BA-method correlated to spirometry outcomes related to airflow obstruction.

Quantitative image analysis

Using the automated BA-method we were able to quantify BA-dimensions with great precision of a large number of airways and BA-pairs. It is not feasible to execute such analysis manually as it is extremely time consuming [22].

We showed that BA-dimensions for bronchial widening correlated to comparable outcomes for the BEST-CT scoring method, especially for the higher cut-off values. The most plausible reason for this difference is that it is difficult for even a trained observer to recognize subtle widening of especially smaller airways (i.e. B_{out}/A between 1-1.5 or B_{in}/A between 0.8 and 1.5) when visually scoring chest CT scans. This observation is in

support of the consensus statement by Alberti et al. to use a conservative cut-off value for inner or outer airway–artery diameter ratio of 1.5 for the diagnosis of bronchiectasis or more when assessing chest CTs by eye-balling to diagnose bronchiectasis [7]. It is likely that we are overestimating the extent and severity of bronchiectasis to some extent as we did not take into account possible progressive bronchial dilatation in relation to age for which reference values are lacking [23, 24]. However, bronchial widening due to aging is also not included in the clinical routine.

For bronchial wall thickening there was a weak positive correlation between BA-dimensions and the BEST-CT scoring method. It is well known that visual scoring of airway wall thickening is difficult as illustrated by low reproducibility scores [12, 25]. It is often not possible for an observer to determine by eye-balling for each BA-pair whether the thickness of the bronchial wall is above or below the cut off value of 0.14 compared to the diameter of the adjacent artery. A great advantage of the automated BA-method is that for each segmental bronchus generation a large number of measurements can be executed to compute the mean bronchial wall thickness for that segment. In the future, the objective assessment of bronchial wall thickness is likely to add relevant objective information that can be used for clinical care [7, 26].

We observed that both bronchial wall thickness and the bronchial lumen diameter correlated weakly to spirometry indicators of airflow obstruction.

Pathophysiologically, we expected that internal diameter of the bronchus as assessed by the BA-method would be the most important CT outcome measure determining the maximal flow for spirometry maneuvers. Airway obstruction in bronchiectasis is often associated with more severe disease, more exacerbations, and more hospital admissions [27, 28]. The internal diameter of bronchi can be reduced for a number of reasons such as inflammation-associated mucosal swelling, folding of the mucosa, mucus impaction, loss of parenchymal attachments, and smooth muscle contraction. From our analysis, we cannot tell which of the five components is most important for the studied patient population. However, it is likely that there will be substantial heterogeneity in the origin of the reduced bronchial lumen and in the contribution of the above-mentioned components to the reduced spirometry indicators of airway obstruction [29-31]. We feel that the most important reason for the weak correlations that we observed between spirometry indicators of airflow obstruction and BA-dimensions can be explained in part by the fact that a chest CT is taken during a static breath hold while spirometry outcomes include also dynamic phenomena which can contribute to airways obstruction.

Limitations

This study has some limitations. Firstly, CT scans were collected retrospectively and acquisition, image reconstruction and lung volume during scanning were not standardized. Lung volume for an inspiratory CT scan is an important determinant for the diagnosis of bronchiectasis as bronchial diameters are more dependent on lung volume compared to the arterial diameter [11]. Moreover, different CT-scanners and protocols (i. e. kernels) were used for different patients which could lead to slightly different BA-method outcomes. This effect is thought to be small as the BA-algorithm corrects for these differences. However, these limitations may have somewhat reduced the sensitivity of our analysis. For future studies and for clinical care it is important to harmonize chest CT imaging protocols across centers and scanners and optimize lung volume during CT acquisition by adequate training and coaching the patient [5, 9].

For our automated BA-method we focused on bronchial dimensions and BA dimensions of BA-pairs and absolute dimensions. When using BA-ratios to detect bronchial widening and thickening is important to keep in mind that pulmonary arterial diameters can be reduced in relation to hypoxic pulmonary vasoconstriction. In addition, there might be patients with early stages of pulmonary hypertension resulting in increased diameters of more central pulmonary arteries. For this reason, it is important to also investigate in the future bronchus related outcome measures independent of their ratio with the adjacent arteries. To do so reference values are needed obtained in healthy populations. It is remarkable that there are to date no well-defined cut-off values to define bronchial (e.a. airway) widening and thickening for the diagnosis of bronchiectasis, especially since Reid et al., already described its importance in 1950 [32]. As radiation doses for chest CTs have come down substantially, and will go down further thanks to developments like the photon counting CT, inclusion of chest CT in population studies to obtain reference values in addition to epidemiological questions might become feasible [33]. Such reference values are needed for the objective diagnosis of airway widening and airway wall thickening.

The BA-method is able to assess the bronchial dimensions with greater precision than the BEST-CT scoring method and then in routine radiology reporting. However, the BA-method currently, does not include in contrast to BEST-CT assessment of mucus plugging, atelectasis and/or consolidations. For the more complete automated analysis of CTs of bronchiectasis patients future versions of the software are needed that also quantifies these important parenchymal changes in patients. However, measurements of bronchial wall thickness can also be considered and estimated of mucus as it is thought to contribute importantly to the bronchial wall as seen on CT.

Clinical Implications

Our study shows that automated BA-method can be used to quantify bronchial dimensions with great precision in bronchiectasis patients that can potentially replace current subjective analysis in the near future for the diagnosis of airways disease and for monitoring of disease progression in daily practice. The information will provide the referring specialist for the first time with an objective assessment of a large number of even small bronchi to phenotype with precision airways disease in the patient and to personalize treatment [34].

In conclusion, we have shown that the automated BA-method is an accurate tool for assessing bronchus and artery dimensions in a large number of bronchus-artery pairs on retrospectively collected chest CTs of bronchiectasis patients. Furthermore, we have observed a stronger correlation between visual assessment, BA software, and lung function when utilizing a cut-off value of 1.5. These BA-method outcomes have potential to replace scoring methods such as the semi-quantitative BEST-CT scoring method for clinical studies and reporting for clinical care.

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References

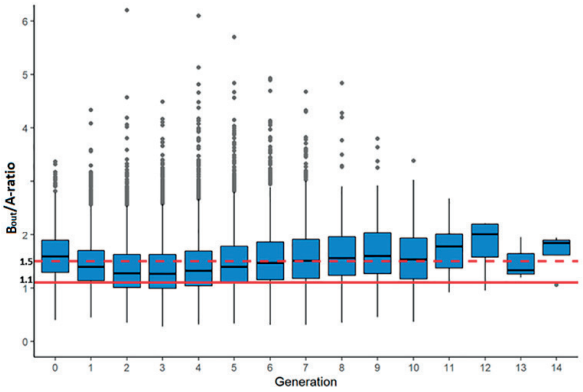
1. Chalmers, J.D., S. Aliberti, and F. Blasi, *Management of bronchiectasis in adults.* Eur Respir J, 2015. **45**(5): p. 1446-62.
2. Bahous, J., et al., *Pulmonary function tests and airway responsiveness to methacholine in chronic bronchiectasis of the adult.* Bull Eur Physiopathol Respir, 1984. **20**(4): p. 375-80.
3. Polverino, E., et al., *European Respiratory Society guidelines for the management of adult bronchiectasis.* European Respiratory Journal, 2017. **50**(3): p. 1700629.
4. Meerburg, J.J., et al., *Diagnosis and quantification of bronchiectasis using computed tomography or magnetic resonance imaging: A systematic review.* Respir Med, 2020. **170**: p. 105954.
5. Tiddens, H., et al., *The radiological diagnosis of bronchiectasis: what's in a name?* Eur Respir Rev, 2020. **29**(156).
6. Hansell, D.M., et al., *Fleischner Society: glossary of terms for thoracic imaging.* Radiology, 2008. **246**(3): p. 697-722.
7. Aliberti, S., 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, 2022. **10**(3): p. 298-306.
8. Rogers, W., et al., *Radiomics: from qualitative to quantitative imaging.* Br J Radiol, 2020. **93**(1108): p. 20190948.
9. Bhalla, A.S., et al., *Imaging protocols for CT chest: A recommendation.* Indian J Radiol Imaging, 2019. **29**(3): p. 236-246.
10. Keistinen, T., et al., *Bronchiectasis: an orphan disease with a poorly-understood prognosis.* Eur Respir J, 1997. **10**(12): p. 2784-7.
11. Meerburg, J.J., et al., *Analysis of Granulomatous Lymphocytic Interstitial Lung Disease Using Two Scoring Systems for Computed Tomography Scans-A Retrospective Cohort Study.* Front Immunol, 2020. **11**: p. 589148.
12. Kuo, W., et al., *Objective airway artery dimensions compared to CT scoring methods assessing structural cystic fibrosis lung disease.* J Cyst Fibros, 2017. **16**(1): p. 116-123.
13. Qianting Lv; Leticia Gallardo Estrella; Eleni-Rosalina Andrinopoulou;, Y.C.J.-P.C.R.M.S.D.C.K.G.N.M.d.B.P.C., *Automatic analysis of bronchus-artery dimensions to diagnose and monitor airways disease in cystic fibrosis.* Press, Submitted.
14. Loebinger, M.R., et al., *Efficacy and safety of TOBI Podhaler in Pseudomonas aeruginosa-infected bronchiectasis patients: iBEST study.* Eur Respir J, 2021. **57**(1).
15. Loebinger, M.R., et al., *Efficacy and safety of tobramycin inhalation powder in bronchiectasis patients with P. aeruginosa infection: Design of a dose-finding study (iBEST-1).* Pulm Pharmacol Ther, 2019. **58**: p. 101834.
16. Jennifer J. Meerburg, A.G.-U., Olivier Dragt, Eleni-Rosalina Andrinopoulou, Mariette, P.C. Kemner van de Corput, Pierluigi Ciet, Gerhild Angyalosi, J. Stuart Elborgn, James D. Chalmers, Michael Tunney, Merleen de Bruine, Harm A.W.M. Tiddens, on behalve of the iABC study group, *Quantitative chest computed tomography scoring technique for bronchiectasis (BEST-CT).* Submitted.
17. Quanjer, P.H., et al., *Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations.* Eur Respir J, 2012. **40**(6): p. 1324-43.
18. Charbonnier, J.P., et al., *Airway wall thickening on CT: Relation to smoking status and severity of COPD.* Respir Med, 2019. **146**: p. 36-41.
19. Nakano, Y., et al., *The prediction of small airway dimensions using computed tomography.* Am J Respir Crit Care Med, 2005. **171**(2): p. 142-6.

20. Lutey, B.A., et al., *Accurate measurement of small airways on low-dose thoracic CT scans in smokers.* Chest, 2013. **143**(5): p. 1321-1329.
21. Koo, T.K. and M.Y. Li, *A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research.* J Chiropr Med, 2016. **15**(2): p. 155-63.
22. Kuo, W., et al., *Diagnosis of bronchiectasis and airway wall thickening in children with cystic fibrosis: Objective airway-artery quantification.* Eur Radiol, 2017. **27**(11): p. 4680-4689.
23. Tan, W.C., 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. **11**(11): p. e0166745.
24. Kim, S.J., et al., *Normal bronchial and pulmonary arterial diameters measured by thin section CT.* J Comput Assist Tomogr, 1995. **19**(3): p. 365-9.
25. Rosenow, T., et al., *PRAGMA-CF. A Quantitative Structural Lung Disease Computed Tomography Outcome in Young Children with Cystic Fibrosis.* Am J Respir Crit Care Med, 2015. **191**(10): p. 1158-65.
26. Diel, R., et al., *Economic burden of bronchiectasis in Germany.* Eur Respir J, 2019. **53**(2).
27. Chalmers, J.D., et al., *The bronchiectasis severity index. An international derivation and validation study.* Am J Respir Crit Care Med, 2014. **189**(5): p. 576-85.
28. Roberts, H.R., et al., *Airflow obstruction in bronchiectasis: correlation between computed tomography features and pulmonary function tests.* Thorax, 2000. **55**(3): p. 198-204.
29. Pompe, E., et al., *Imaging-derived biomarkers in Asthma: Current status and future perspectives.* Respir Med, 2023. **208**: p. 107130.
30. Dunican, E.M., *Seeing the forest for the trees: fractal dimensions measure COPD airway remodeling.* J Clin Invest, 2018. **128**(12): p. 5203-5205.
31. Dunican, E.M., et al., *Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction.* J Clin Invest, 2018. **128**(3): p. 997-1009.
32. Reid, L.M., *Reduction in bronchial subdivision in bronchiectasis.* Thorax, 1950. **5**(3): p. 233-47.
33. Willemink, M.J., et al., *Photon-counting CT: Technical Principles and Clinical Prospects.* Radiology, 2018. **289**(2): p. 293-312.
34. Schork, N.J., *Personalized medicine: Time for one-person trials.* Nature, 2015. **520**(7549): p. 609-11.

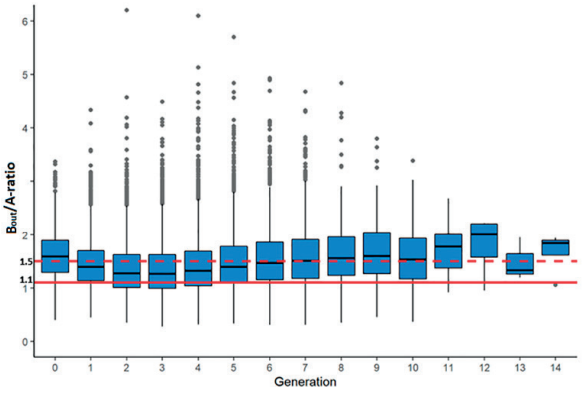
Supplementary Material

Table of contents - supplementary

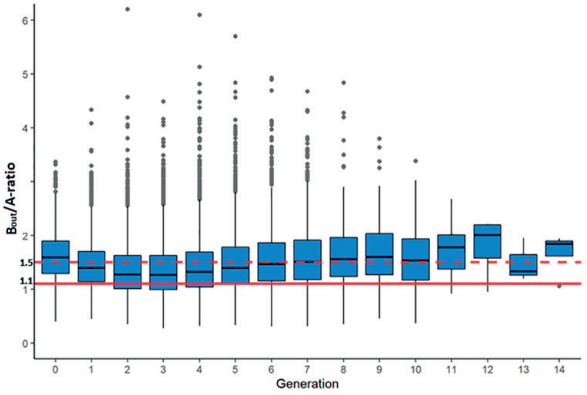
Graph A



Graph B

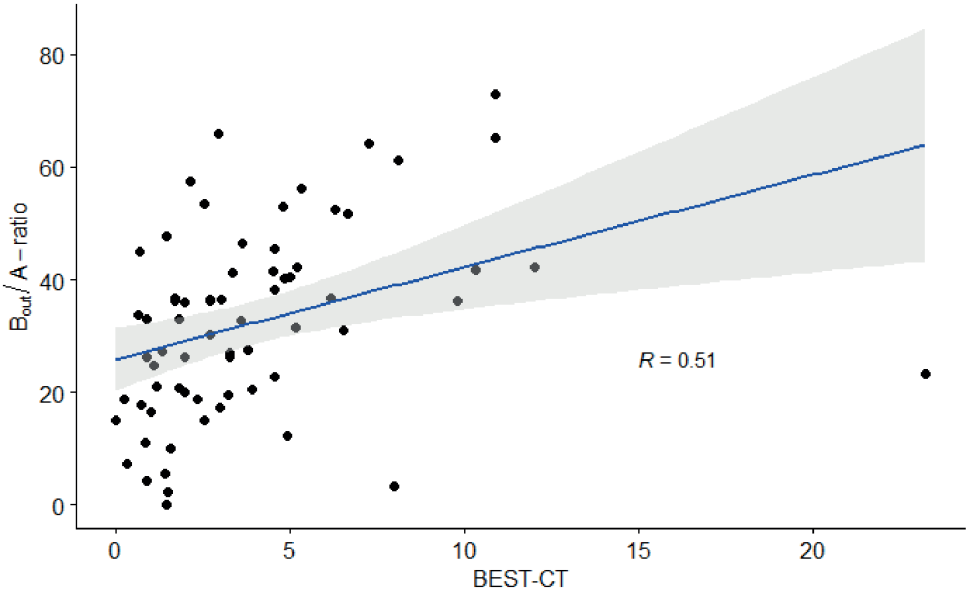


Graph C



Supplemental Figure 1. Bronchus-artery ratio's in all measurable generations ($G_{1\text{-}14}$).

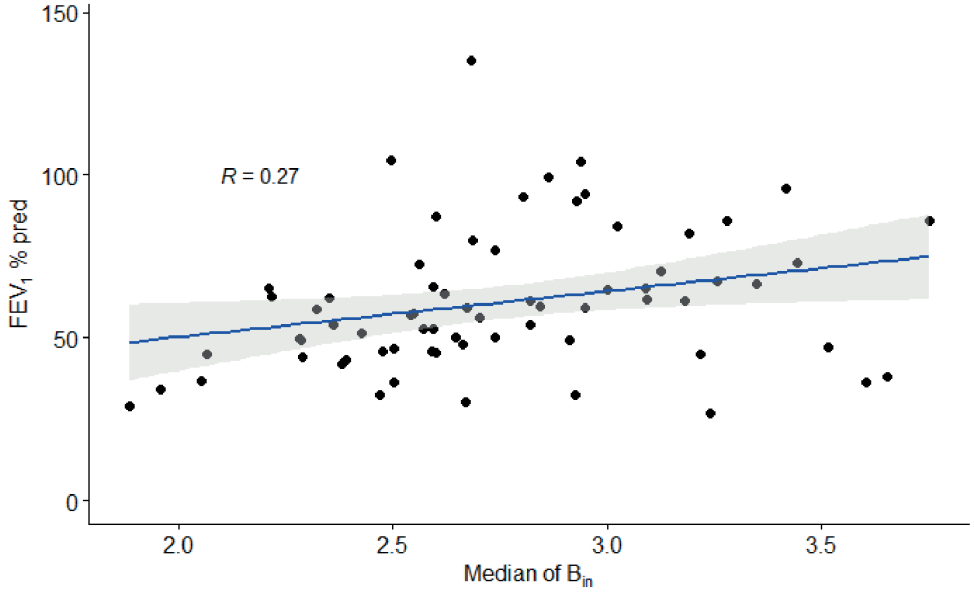
This figure shows the B_{out}/A, B_{in}/A and B_{wt}/A-ratio's starting at the segmental level (generation 0). The grey dots indicate individual bronchus-artery ratios. The blue boxes indicate the median and interquartile range (25^{th}-75^{th} percentile). **Graph A** shows the B_{out}/A-ratio per generation. The bold red line indicates the B_{out}/A cut-off of ≥1.1 and the red dotted line the cut-off of ≥1.5 for brochial widening. **Graph B** shows the B_{in}/A-ratio for generation 1 to 6. The bold red line indicates the B_{in}/A-ratio cut-off of ≥ 0.8 and the red dotted line the cut-off of ≥ 1.5. **Graph C** shows B_{wt}/A-ratio. The bold red line indicates the B_{wt}/A cut-off of 0.14 per generation.



Supplemental Figure 2. Correlation between BEST-CT versus the automatic BA-method (B_{out}/A-ratio)

This figure shows the correlation for bronchial widening between the two different scoring systems: BronchiEctasis Scoring Technique (BEST-CT) outcomes (% bronchiectasis) versus automatic BA-method in generations ($G_{1\text{-}6}$) for bronchial widening. Bronchial widening for automatic BA-method was defined as B_{out}/A-ratio ≥ cut-off of ≥1.5. The black dots indicate the individual measurements and the gray box indicate the 95% confidence interval.

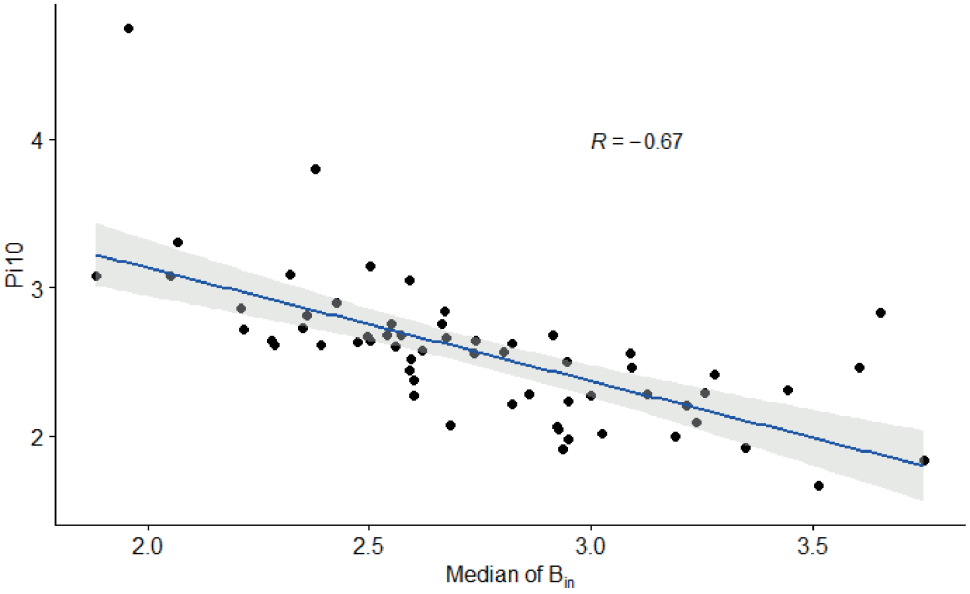
R = correlation coefficient; BEST-CT = BronchiEctasis Scoring Technique.



Supplemental Figure 3. Correlation between spirometry parameter (FEV_1) versus the bronchial inner diameter (B_{in} derived from automatic BA- method) in limited generations (G_{1-6}).

This figure shows the correlation between the spirometry parameter FEV_1 versus the median of B_{in} derived from the automatic BA-method. The black dots indicate the individual measurements and the gray box indicate the 95% confidence interval.

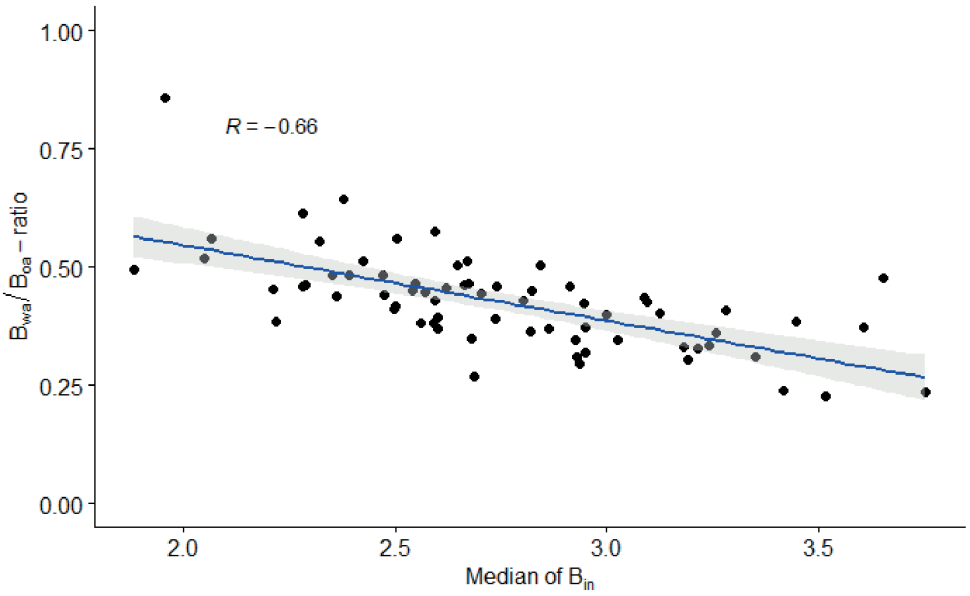
FEV_1, %pred = forced expiratory volume in 1 second as a percentage of predicted forced expiratory volume in 1 second; R = correlation coefficient**.**



Supplemental Figure 4. Correlation between bronchial inner diameter (B_{in}, derived from automatic BA-method) versus airway wall thickening (P_{i10}, derived from automatic BA-method) in limited generations (G_{1-6}).

This figure shows the correlation between the median of bronchial inner (B_{in}) derived from the automatic BA-method versus airway wall thickening described as P_{i10} derived from automatic BA-method in limited generations (G_{1-6}). P_{i10} is defined as the square root of the wall area for a hypothetical airway with an internal perimeter of 10 mm. The black dots indicate the individual measurements and the gray box indicate the 95% confidence interval.

R = correlation coefficient



Supplemental Figure 5. Correlation between bronchial inner diameter (B_{in}, derived from automatic BA-method) versus bronchial wall thickening (B_{wa}/B_{oa}, derived from automatic BA-method) in limited generations (G_{1-6}).

This figure shows the correlation between the median of bronchial inner (B_{in}) derived from the automatic BA-method versus bronchial wall thickening described as B_{wa}/B_{oa} derived from automatic BA-method in limited generations (G_{1-6}). B_{wa}/B_{oa} is defined as the ratio between the wall area B_{wa} and the area defined by the outer airway (B_{oa}) (B_{wa}/B_{oa}). black dots indicate the individual measurements and the gray box indicate the 95% confidence interval.

R = correlation coefficient

Supplementary Table 1. Correlation between BEST-CT versus the automated BA-method (Bout/A-ratio) in limited generations (G1-6).

Segmental generation	Average count of BA ratios	Average count of bronchi
1	21	29
2	41	50
3	56	67
4	52	65
5	35	46
6	21	30

The average of bronchus-artery (BA) ratio's and bronchi per segmental generation for limited generations (G1-6).

Table 2. Correlation between BEST-CT (%BE, %BWT) versus the automatic BA-method ratios (B_{out}/A, B_{in}/A and B_{wt}/A) in all measurable generations (G_{1-14}). Sensitivity analysis.

	Automatic BA-method for bronchial widening			
	B_{out}/A≥1.1	**B_{out}/A≥1.5**	**B_{in}/A≥0.8**	**B_{in}/A≥1.5**
%BE_BEST-CT	R = 0.31 [0.04, 0.54)	R= 0.52 [0.32, 0.71]	R=0.21 [-0.03, 0.47]	R=0.47 [0.24, 0.68]
	Automatic BA method for bronchial wall thickening (B_{wt}/A≥0.14)			
	B_{wt}/A≥0.14			
%BWT_BEST-CT	R=0.28 [0.06, 0.48]			

Bronchial widening were defined as B_{out}/A-ratio ≥ cut-off of 1.1 and ≥ 1.5 and B_{in}/A cut-off of ≥ 0.8 and ≥ 1.5 Bronchial wall thickening was defined as B_{wt}/A-ratio ≥ cut-off of 0.14.

Note that all the results are shown as Spearman (or Pearson) correlation coefficient (r) and [95% confidence interval].

Table 3. Results of linear regression analysis: Spirometry parameters versus the automatic BA-method of bronchial widening (described as B_{out}/A) in limited generations (G_{1-6}) and all measurable generations (G_{1-14}). Sensitivity analysis.

	G_{1-6}			G_{1-14}		
	Estimates	Standard Error	Adjusted P-values	Estimates	Standard Error	Adjusted P-values
FEV_1, %pred	15.88	12.80	0.44	13.56	12.37	0.56
FEV_1/FVC, %pred	-2.06	8.17	1.00	-1.04	7.87	1.00
Log ($FEF_{25-75\%}$, %pred)	-0.01	0.36	1.00	-0.01	0.35	1.00

This table shows the regression analysis for spirometry (FEV_1% predicted, FEV_1/FVC% predicted and log $FEF_{25-75\%}$ predicted) versus the median of B_{out}/A.

FEV_1, %pred= forced expiratory volume in 1 second as a percentage of predicted forced expiratory volume in 1 second; FVC= forced vital capacity as a percentage of predicted forced vital capacity; $FEF_{25-75\%}$= forced expiratory flow between 25 and 75% of vital capacity as a percentage of predicted forced expiratory flow.

Table 4. Results of linear regression analysis: Spirometry parameters versus the automatic BA-method of bronchial widening (described as B_{in}/A) in in limited generations (G_{1-6}) and all measurable generations (G_{1-14}). Sensitivity analysis.

	G_{1-6}			G_{1-14}		
	Estimates	Standard Error	Adjusted P-values	Estimates	Standard Error	Adjusted P-values
FEV_1, %pred	35.08	13.82	0.07	33.91	13.73	0.08
FEV_1/FVC, %pred	11.02	9.08	0.69	11.58	8.98	0.61
Log ($FEF_{25-75\%}$, %pred)	0.42	0.41	0.93	0.42	0.41	0.89

This table shows the regression analysis for spirometry (FEV_1% predicted, FEV_1/FVC% predicted and log $FEF_{25-75\%}$ predicted) versus the median of B_{in}/A.

FEV_1, %pred = forced expiratory volume in 1 second as a percentage of predicted forced expiratory volume in 1 second; FVC = forced vital capacity as a percentage of predicted forced vital capacity; $FEF_{25-75\%}$= forced expiratory flow between 25 and 75% of vital capacity as a percentage of predicted forced expiratory flow.

Table 5. Results of linear regression analysis: Spirometry parameters versus the automatic BA-method of bronchial wall thickening (described as B_{wt}/A) in limited generations (G_{1-6}) and all measurable generations (G_{1-14}). Sensitivity analysis.

	G_{1-6}			G_{1-14}		
	Estimates	Standard Error	Adjusted P-values	Estimates	Standard Error	Adjusted P-values
FEV_1, %pred	-67.12	27.83	0.08	-67.71	27.24	0.08
FEV_1/FVC, %pred	-64.54	16.22	<0.01*	-60.43	16.13	<0.01*
Log ($FEF_{25-75\%}$, %pred)	-1.97	0.77	0.08	-1.93	0.76	0.082

This table shows the regression analysis for spirometry (FEV_1% predicted, FEV_1/FVC% predicted and log $FEF_{25-75\%}$ predicted) versus the median of B_{wt}/A.

The significant p-value is indicated by *. FEV_1, %pred = forced expiratory volume in 1 second as a percentage of predicted forced expiratory volume in 1 second; FVC= forced vital capacity as a percentage of predicted forced vital capacity; $FEF_{25-75\%}$= forced expiratory flow between 25 and 75% of vital capacity as a percentage of predicted forced expiratory flow.

Table 6. Results of linear regression analysis: Spirometry parameters versus the automatic BA- method of bronchial wall thickening (described as B_{wa}/B_{oa}) in limited generations (G_{1-6}) and all measurable generations (G_{1-14}). Sensitivity analysis.

	G_{1-6}			G_{1-14}		
	Estimates	Standard Error	Adjusted P-values	Estimates	Standard Error	Adjusted P-values
FEV_1, %pred	-103.15	28.64	0.09	-107.03	28.54	<0.01*
FEV_1/FVC, %pred	-71.26	17.58	0.09	-72.83	17.57	<0.01*
Log ($FEF_{25-75\%}$, %pred)	-2.33	0.84	0.08	-2.47	0.84	0.04

This table shows the regression analysis for spirometry (FEV_1% predicted, FEV_1/FVC% predicted and log $FEF_{25-75\%}$ predicted) versus the median of B_{wa}/B_{oa}.

The significant p-value is indicated by *. FEV_1, %pred = forced expiratory volume in 1 second as a percentage of predicted forced expiratory volume in 1 second; FVC= forced vital capacity as a percentage of predicted forced vital capacity; $FEF_{25-75\%}$= forced expiratory flow between 25 and 75% of vital capacity as a percentage of predicted forced expiratory flow.

Chapter 4

Automatic CT Analysis of Structural Lung Abnormalities in 609 Bronchiectasis Patients: Insights from the EMBARC Registry

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***Shared first authorship based on equal contribution**
****Shared senior authorship based on equal contribution.**

Submitted

Abstract

Aims: Dilatation, thickening of the bronchi and mucus plugs (MP) are key CT features of bronchiectasis patients. Manual scoring systems are used to quantify these structural lung abnormalities, but are time consuming and require training. AI-based algorithms have been developed to measure bronchus and artery (BA) dimensions and the number of MP. We aimed to analyse CTs from EMBARC, the European Bronchiectasis Registry.

Methods: CTs from 609 EMBARC patients were analysed. LungQ-BA automatically segments the bronchial tree, identifies the segmental bronchi (G_0) and distal airway generations (G_1, G_2, G_3, etc.) For each BA-pair, the following dimensions were quantified: diameters of bronchial outer edge (B_{out}), inner edge (B_{in}), wall thickness (B_{wt}), and artery (A). From these dimensions, BA-ratios are computed: B_{out}/A, B_{in}/A, B_{wt}/A, and bronchial wall area/ outer area (B_{wa}/B_{oa}). LungQ-MP automatically segments the bronchial tree, detects the total MP number.

Results: Bronchial dilatation and thickening were observed in 73% and 49% of all BA-pairs, respectively. Older patients and those with longer disease duration exhibited more pronounced bronchial and mucus abnormalities. MP-count was significantly associated with *Pseudomonas aeruginosa* infection, severe exacerbations and primary ciliary dyskinesia. Ppost-infective cases showed less wall thickening. Patients with asthma and/or COPD overlap syndromes had less bronchial dilatation but more wall thickening.

Conclusion: The automatic analysis of CT scans from EMBARC participants shows severe dilatation and thickening and a wide range of severity and extent. Radiological disease was more severe in patients with chronic airway infection, severe exacerbations and longer disease duration.

Introduction

Bronchiectasis is characterized by the presence of abnormal permanent bronchial dilatation on a chest computed tomography (CT) scan and a clinical syndrome of chronic cough, sputum production and recurrent infections [1]. Bronchiectasis can be caused by a wide range of disorders including primary or secondary immune deficiencies, primary ciliary dyskinesia (PCD), post-infectious causes and other conditions such as chronic aspiration or connective tissue disease [2]. However, the majority of patients even in specialist centres are still classified as idiopathic bronchiectasis [3]. Chest CT is considered the gold standard for the visual diagnosis of bronchiectasis [4, 5]. The most widely accepted definition of bronchiectasis by radiologists, as observed by visual inspection on chest CT, is a chronic dilatation of the bronchus that is larger compared to the adjacent artery (i.e. bronchus-artery ratio>1), lack of tapering, and visibility of an airway in the periphery of the lung [6-9]. Other structural abnormalities that can be observed on chest CTs of bronchiectasis patients are mucus plugs, airway wall thickening, atelectasis, and parenchymal abnormalities such as consolidations [7, 10]. For today's clinical care, the presence and extent of bronchiectasis patients is mostly subjective, and does not include any quantitative assessment of the above mentioned structural lung abnormalities. Moreover, the absence of standardized chest CT image acquisition methods can affect the accuracy and precision of bronchiectasis diagnosis [7, 11, 12]. The assessment of disease severity and disease activity in patients with bronchiectasis has emerged as a key factor in disease assessment[13]. The lack of objective methods to quantify CT abnormalities limits the ability of CT to be used to risk stratify patients with bronchiectasis and to assess anatomical changes in the disease course including response to treatment.

The European Multi-centre Bronchiectasis Audit and Research Collaboration (EMBARC) registry was established in 2015 and currently represents the largest bronchiectasis dataset in the world. Embedded within the EMBARC registry are a number of substudies including an imaging subcohort in which baseline chest CT scans are collected alongside detailed clinical data.

Several (semi)quantitative manual scoring systems have been developed to assess CT scans of bronchiectasis patients [14-16]. The Bronchiectasis Scoring Technique for CT (BEST-CT) is a validated quantitative scoring method to quantify structural lung damage in bronchiectasis disease patients [17]. BEST-CT was shown to be reproducible to phenotype and measure the severity and extent of the structural lung abnormalities in prior studies [10, 17, 18]. BEST-CT was used to assess the severity and extent of structural lung disease components in 524 EMBARC patients [17]. It was shown that the structural lung abnormalities were highly heterogeneous. Furthermore,

strong relationships between radiological disease and clinical features were shown. It was concluded that CT analysis could be a useful tool for clinical phenotyping of bronchiectasis patients. While an important proof of concept, the disadvantages of the BEST-CT system is that it requires additional training of the observer, and that it is time consuming, taking over 45 minutes for the analysis of a single CT scan. More recently, a fully automated algorithm for the detection and quantification of BA-pairs was developed using state-of-the-art artificial intelligence (AI) techniques [19, 20]. It has been shown that the automatic BA-analysis was able to detect and quantify a large number of BA-pairs in a cohort of 69 bronchiectasis patients participating in a clinical trial [21]. Furthermore, moderate correlations were observed between BA-dimensions and comparable outcomes for the BEST-CT scoring [21]. In addition to bronchial dimensions, mucus plugging was also shown to be an important structural abnormality [17]. The presence of mucus plugs in bronchiectasis disease is associated with inflammation and infection, resulting in airflow obstruction and impaired lung function [22]. Like for the BA-analysis, an AI based algorithm was developed to quantify the number and volume of airway-occluding mucus plugs throughout the entire bronchial tree. Therefore, the automatic BA-analysis and mucus plug (MP)-analysis could be of great value for rapidly evaluating structural disease and markers of disease activity.

The aim of the current study is to analyse a large number of chest CTs from EMBARC patients using the BA-analysis and MP-analysis, and to investigate associations with clinical outcomes.

Materials and methods

Study population

We collected clinical data and CTs from patients enrolled in the EMBARC registry. Details of the EMBARC data collection protocol and baseline data from the EMBARC registry have been published previously [23, 24]. Key inclusion criteria for patients to be included in the EMBARC registry are: patients with a primary clinical diagnosis of bronchiectasis consisting of (1) a clinical history consistent with bronchiectasis and (2) CT scan demonstrating bronchiectasis per judgment of the including centre. Key exclusion criteria for EMBARC registry are (1) bronchiectasis due to known cystic fibrosis (CF) (2) age < 18 years and (3) patients who are unable or unwilling to provide informed consent. A complete list of in- and exclusion criteria was described previously [23]. For the current CT sub study, eight bronchiectasis centres in six countries were included: Rotterdam, The Netherlands; Dundee, London and Cambridge, UK; St Niklaas, Belgium; Monza, Italy; Haifa, Israel; and Paris, France (Figure 1). Each centre

was asked to collect randomly CTs from a sub selection of 50 to 100 patients within their cohort. Moreover, for each patient, the centres selected the chest CT-scan that was performed closest to the time of enrolment in the EMBARC registry (within a maximum time interval of 4 years).

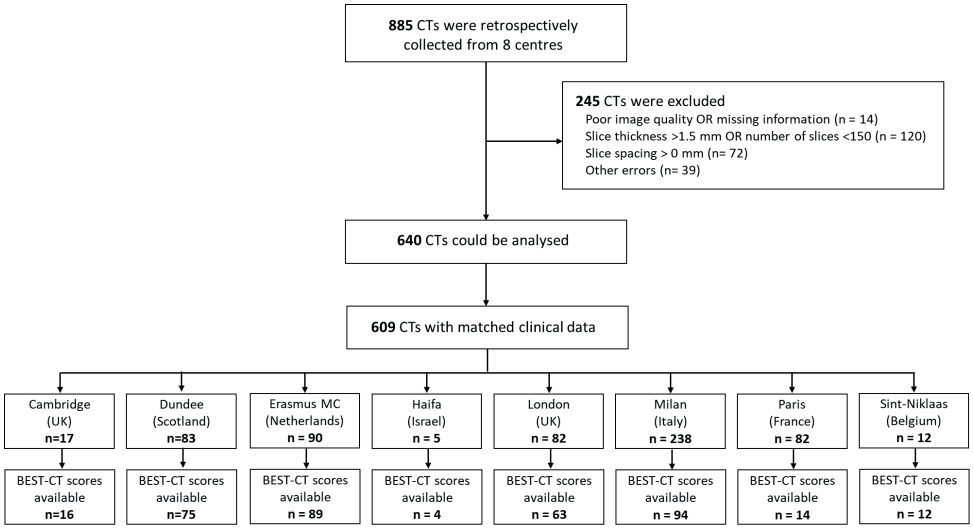

Figure 1. Flow chart

In parallel to the primary bronchiectasis registry, EMBARC has a European *non-tuberculous mycobacterial* (NTM) registry sub study, which collects additional data from patients meeting the IDSA/ATS criteria for NTM active infection [25]. The NTM registry was used to enrich our dataset with CTs from patients with active NTM infection, for which reason some centres were asked to include additional NTM patients. This oversampling was performed to ensure sufficient statistical power to investigate this relevant clinical determinant (NTM) due to its relatively low prevalence in European centres [26].

Clinical parameters

To generate relevant patient descriptives for the cohort, we extracted the following data from the EMBARC registry: demographic characteristics, previous medical history, comorbidities, spirometry, hospital admission in the 1 year before inclusion in the study, microbiology, and severity of disease as reflected by the Bronchiectasis Severity Index (BSI) and FACED score (FEV_1% predicted, age, chronic colonization by PsA, radiological extent of disease, and dyspnoea [27, 28].

Furthermore, we extracted the underlying aetiology of bronchiectasis which is recorded in the EMBARC registry based on testing recommendations by European Respiratory Society guidelines. Ten different aetiology groups were defined based on the available categories in the registry and the sample sizes per group: (1) idiopathic bronchiectasis; (2) allergic bronchopulmonary aspergillosis (ABPA); (3) asthma; (4) primary/secondary immunodeficiency (5) connective tissue disease, rheumatoid arthritis (RA) and inflammatory bowel disease; (6) chronic obstructive pulmonary disease (COPD); (7) NTM infection; (8) other disease (including Mounier-Kuhn syndrome, yellow nail syndrome, Young's syndrome, CFTR-related disorders, aspiration and gastroesophageal reflux disease); (9) post infectious bronchiectasis (including post tuberculosis); and (10) PCD.

Additionally, we extracted from the EMBARC database whether patients have a co-diagnosis of asthma and/or COPD in addition to the recorded primary aetiology of the bronchiectasis.

Finally, we extracted the duration of diseases from the EMBARC registry. In the registry patients are categorized by their known duration of bronchiectasis disease in 5 different groups (0-5 years; 5-10 years; 10-15 years; 15-20 years and ≥20 years). Hospital admissions due to pulmonary exacerbations in the last year were categorized as: none, one, or two or more.Furthermore, patients were categorized by blood eosinophil counts, either normal or elevated (≥300 cells/mL) [29].

CT transfer and quality assessment

The Erasmus MC LungAnalysis core laboratory (Rotterdam, the Netherlands) provided participating centres with a procedure to verify the pseudonymity of CT images and facilitated safe data transfer of pseudonymized CT scans from participating hospitals to LungAnalysis. Quality assessment of transferred CTs was executed by the LungAnalysis laboratory. CT scans were included in this sub study when they met the following requirements: (1) correct digital format (correct DICOM headers), (2) sufficient inspiratory lung volume as defined by a round shape of the trachea and presence of lung parenchyma between the heart and sternum, (3) complete display of the lungs, (4) no artifacts or artifacts with minimal effect on the visualization of the lungs, (5) no missing slices or irregular spacing between slices, (6) slice thickness of 1.5 mm or below.

Bronchus and artery analysis

The automated BA analysis was performed on all CTs that met the technical requirements for the algorithm using LungQ version 3.1.0 (Thirona, Nijmegen, The Netherlands). The automatic BA-analysis starts by automatically detecting and segmenting the bronchial tree on an inspiratory CT scan. Next, for each bronchus

starting at the segmental bronchus (G_0) and for higher generations ($G_{1,2,3...}$) the adjacent artery is identified. Next, for each identified BA-pair and segmental bronchus generation, the following dimensions are computed perpendicular to the longitudinal bronchus or artery axis (figure 1): Bronchial inner diameter (B_{in}); Bronchial outer diameter (B_{out}); Bronchial wall thickness (B_{wt} (=(B_{out}-B_{in})/2)), bronchial wall area (B_{wa}), Bronchial outer area (B_{oa}) and Artery diameter (A). The BA-analysis utilizes a proprietary intensity profile quantification algorithm that allows for sub-resolution quantification of bronchial wall thickness. The algorithm quantifies each individual bronchus in cross-section perpendicular to the local bronchial direction by calculating the bronchial dimensions in a multitude of radial intensity profiles with a sampling distance of higher resolution than the resolution of the scan. For each bronchial generation G_0 and higher, the BA-dimensions of each individual bronchial branch is computed as the average of all measurements within that branch. The following BA-ratios are calculated: B_{out}/A, B_{in}/A, B_{wt}/A, and B_{wa}/B_{oa}.

The cut-off values to determine bronchial dilatation and bronchial wall thickening are based on the automated BA-method of a previously manual annotated dataset of chest CTs from patients with CF and from normal CTs of age matched control subjects [30]. As there is no universally accepted definition for bronchial dilatation [7], we use a cut off value for B_{out}/A of ≥ 1.1 [19] and a more conservative cut off value of ≥ 1.5 for visual detectable bronchiectasis[31] as suggested in a consensus publication based on a Delphi process by an international taskforce of experts to develop recommendations and definitions for bronchiectasis. Furthermore, we use cut off values for B_{in}/A [32] ratio for bronchial dilatation of ≥ 0.8 and ≥1.5[31]. Bronchial wall thickening was defined as B_{wt}/A-ratio ≥0.14 [32]and as of B_{wa}/B_{oa} >0.37 (data on file).

Mucus plug analysis

The automatic MP-analysis was performed using the same LungQ version on all CTs that met the technical requirements. Bronchus-occluding mucus plugs throughout the entire bronchial tree were quantified, measuring their number and volume. In addition, the number of lobes containing one or more mucus plugs was determined. The algorithm identifies full mucus obstructions with clear proximal and distal airways, providing both location and volumetric assessments. The segmentation combines seed-based and voxel-based methods, providing detection and quantification of mucus plugs along the entire bronchi, including the peripheries. The algorithm provides output as the number of detected mucus plugs the number of segments with one or more plugs and volumes of the mucus plugs (mL).

BEST-CT analysis

To allow comparison between the automatic analysis and visual scores we collected BEST-CT metrics of those CTs included in the current study that were also previously scored manually [17]. BEST-CT is a morphometry based visual scoring system for bronchiectasis disease. In short: a grid is placed on 10 equally spaced axial chest-CT slices between lung apex and base. Each grid box is annotated by a trained and certified observer for the presence of structural lung abnormalities [18]. Each grid cell that contains at least 50% coverage of the lung is scored using the following hierarchical system (highest to lowest priority): 1. Atelectasis/consolidation (ATCON), 2. bronchiectasis with mucus plugging (BEMP), 3. bronchiectasis without mucus plugging (BEwMP), 4. Airway wall thickening (AWT), 5. Mucus plugging without bronchiectasis (MP), 6. Ground-glass opacities (GGO), 7. Bullae (BUL), 8. Healthy airways (HA) and 9. Healthy parenchyma (HP).

The following composite BEST-CT scores were computed from the component scores and used for this study:

Total bronchiectasis (%TBE) = %BEMP + %BEwMP

Total mucus plugging (%TMP) = %BEMP + %MP

Total of inflammatory CT-characteristics (%TInF) = %ATCON + %BEMP + %MP

Intra- and inter-observer reliability data are available (Table S2) [17].

Statistical analysis

Descriptive statistics of patient characteristics are displayed as median (interquartile range, IQR), mean (standard division, SD) or number (percentage), as appropriate. The large number of BA-ratios measured per CT were summarized as the median of BA-ratios in $G_{1\text{-}6}$ for each CT. The associations between BA and MP metrics and the following clinical parameters were investigated using multivariable linear regression analysis: age, gender, length of disease, FEV_1 %pred, microbiology, smoking status, hospital admissions, aetiology, co-diagnosis of asthma and/or COPD, eosinophil count, BSI and FACED. These investigated clinical parameters were largely the same as were investigated in the previous study investigating the associations between the BEST-CT visual scoring and clinical parameters [17]. For categories we also performed F-test for overall effects. Sensitivity analysis was performed for MP count and volume outcomes assuming generalized linear models with a non-standard response distribution (Tweedie family[33]). For the comparison between BEST-CT scores and BA and MP metrics, we used Spearman correlation coefficients because of the skewed data distribution. A

correlation coefficient lower than 0.2 was rated as very weak, 0.2-0.4 as weak, 0.4-0.6 as moderate, 0.6-0.8 as strong, and 0.8-1 as excellent[34]. All statistical analysis was done using R (version 4.3.2). Correction for multiple testing was not performed. Statistically significant results were defined as a p-value less than 0.05.

Table 1. Patient characteristics

Demographics	**Value**
Number of analyzed CT scans	609
Age (Years)	60.7 (15.3)
Gender (Male/Female)	190 (31%) / 419 (69%)
BMI	24.0 (5.7)
Country	
Rotterdam, The Netherlands	90 (15%)
St Niklaas, Belgium	12 (2%)
London, United Kingdom	82 (13%)
Dundee, United Kingdom	83 (14%)
Cambridge, United Kingdom	17 (3%)
Haifa, Israel	5 (1%)
Monza, Italy	238 (39 %)
Paris, France	82 (13%)
History of Bronchiectasis[x]	
< 5 years	228 (37%)
5 – 9 years	119 (19%)
10-14 years	70 (11%)
15-20 years	40 (7%)
>20 years	126 (20%)
Underlying Etiology	
Idiopathic	290 (47%)
Post Infective	92 (15%)
Other diseases	50 (8%)
ABPA	27 (4%)
Primary/secondary immunodeficiency	35 (6%)
NTM	29 (5%)
COPD	17 (3%)
Primary Ciliary Dyskinesia	33 (5%)
CTD / RA / IBD	24 (4%)
Asthma	18 (3%)
Co-diagnosis of Asthma and/or COPD	

Table 1. Continued

Demographics	Value
Asthma	149 (24%)
COPD	75 (12%)
Spirometry	
FEV_1, %pred	80.1% (24.9%)
FVC, %pred	94.0% (23.5%)
Smoking status	
Never	355 (58%)
Ex	218 (36%)
Current	36 (6%)
P. aeruginosa infection	226 (37%)
NTM infection ^	100 (17%)

This table shows the patient characteristics at the time of enrolment in the EMBARC registry. Data is presented in mean (standard deviation, SD) or number (percentage). BMI = body mass index. FVC= forced vital capacity; FEV1= forced expiratory volume in 1 second; ABPA = Allergic bronchopulmonary aspergillosis; CTD = connective tissue disease; RA = Rheumatoid arthritis; IBD = inflammatory bowel disease; COPD = Chronic obstructive pulmonary disease; NTM = nontuberculous mycobacteria. x History of Bronchiectasis data of 32 patients are missing. ᵂ BMI data of 183 patients are missing. ^ NTM infection data of 17 patients are missing.

Results

CT collection and study population

We collected 854 CT scans from 8 centres. 245 CTs did not meet the technical requirements for the automatic analysis (Figure 1). 30 CTs did not have complete matched clinical data. Hence, 609 inspiratory CTs were successfully analysed using both BA-analysis and MP-analysis. The manual BEST-CT scores were available for 364 of these 609 patients. Patient characteristics and aetiology of bronchiectasis disease of the selected group are shown in Table 1. 69% of patients were female (n = 419) and mean age was 60.7 (SD, 15.3, range 18-93) years. In 290 patients (47%) the cause of bronchiectasis disease was classified as idiopathic, in 93 (15%) as post-infectious, respectively (Table 1). 226 (37%) patients had a history of infection with *Pseudomonas aeruginosa* and 100 (17%) with *NTM*. The median time between the CT scan and enrolment in the EMBARC registry was 338 days (IQR, 101-771 days).

Bronchus and artery analysis

A total of 135,489 BA-pairs were detected from segmental generations G_0 up to G_{18}. On average, a mean of 223 (SD, 101) BA-pairs per CT were detected. The highest number of BA-pairs per CT was detected in segmental generation G_3 (Figure S1). A

total of 124,382 (92% of all BA-pairs) were detected in segmental generations G_1-G_6, which generations were used for further statistical analysis.

The median (IQR) B_{out}/A, B_{in}/A, B_{wt}/A, and B_{wa}/B_{oa} for $G_{1\text{-}6}$ were 1.34 (1.07, 1.71), 1.04 (0.81, 1.35), 0.13 (0.1, 0.2), and 0.37 (0.29, 0.47), respectively (Figure 2). B_{out}/A >1.1 or >1.5 (indicating bronchial dilatation) were observed in 73% and 39% of all BA-pairs, respectively. Concerning bronchial wall thickening, a B_{wt}/A>0.14 was observed in 49% of all BA-pairs and B_{wa}/B_{oa} >0.37 was observed in 51% of all BA-pairs.

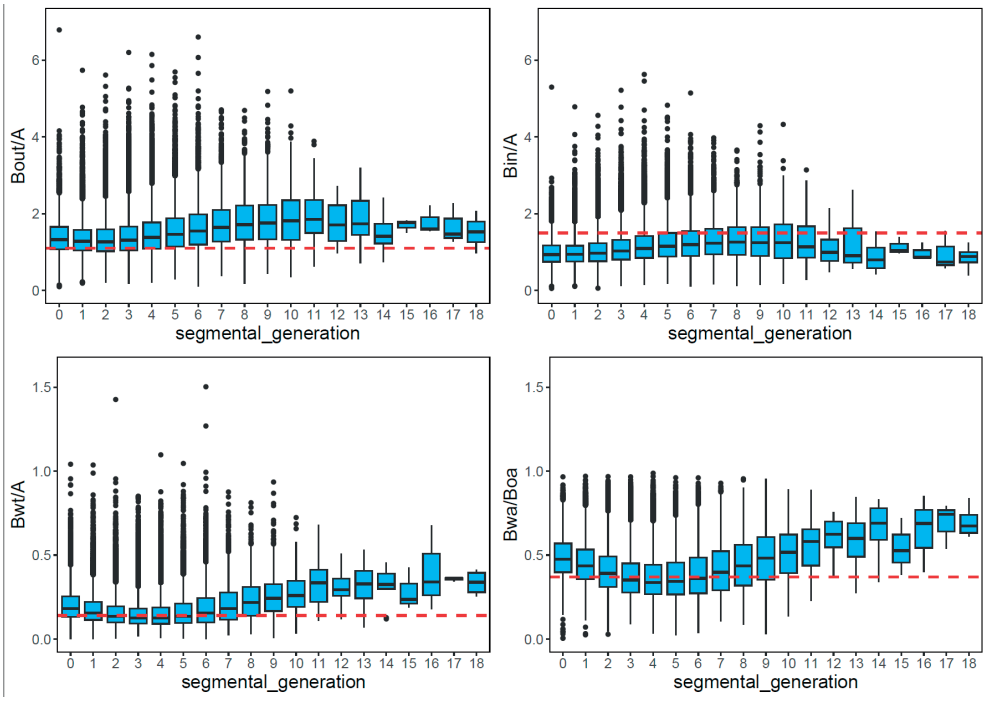

Figure 2. Boxplots of BA-ratios

The red dotted lines represent the computed cut-off values for bronchial dilatation. For B_{out}/A this cut-off is 1.1 and for B_{in}/A 0.8. For bronchial wall thickening the cut-off value for B_{wt}/A is 0.14 and for B_{wa}/B_{oa} 0.37. B_{out} = diameter of bronchus outer edge; B_{in}= diameter of bronchus inner edge; A = diameter of artery; B_{wt} = bronchus wall thickness; B_{wa}/B_{oa} = bronchial wall area/bronchial outer area.

Mucus plug analysis

A total of 12,385 mucus plugs were detected on 533 (83%) CTs with a median count of 8 (2, 25) (Figure 3) and a volume of 0.44 (0.06, 1.64) mL (Figure S2). In 101 (17%) patients, no mucus plug could be detected.

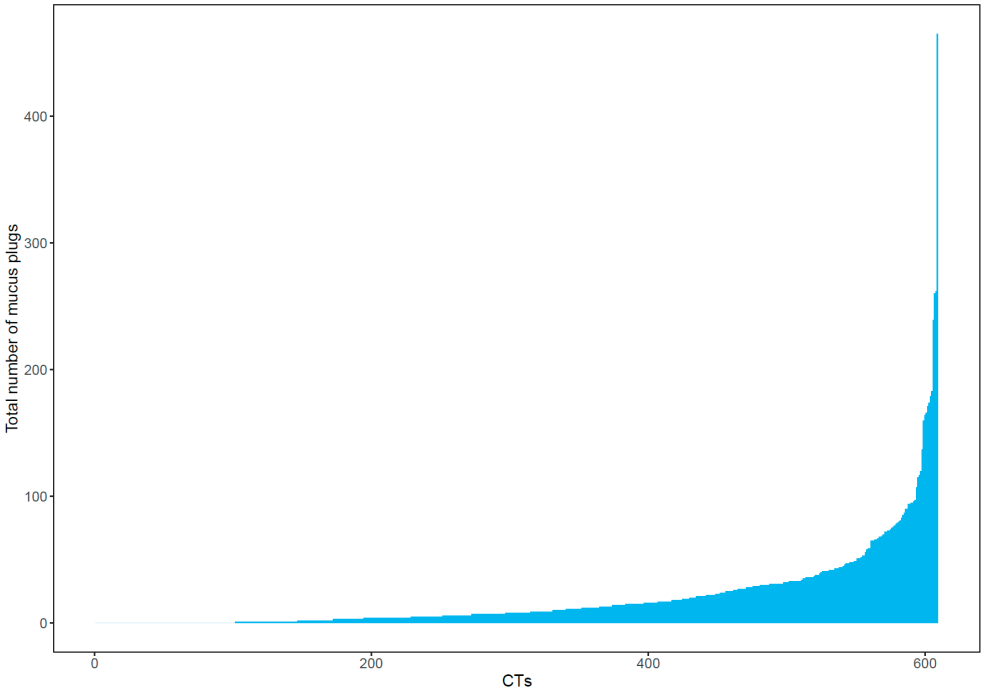

Figure 3. Distribution of mucus plug count

This figure shows the number of mucus plugs detected on the chest CT. There is a wide range between patients from no mucus plugs to 465 mucus plugs per CT. Note that 101 (17%) patient did not have any detectable plug.

Clinical characteristics and BA and MP metrics

Associations between BA and MP-metrics are shown in Table 2. A significant and positive association was observed between B_{out}/A (p=0.002), B_{in}/A (p = 0.005), MP count (P=0.002), and age. Female gender showed higher values for B_{out}/A (p = 0.017), and B_{wt}/A (p = 0.022). A longer length of disease (especially between 15-20 years) showed more severe B_{out}/A, B_{wt}/A and MP count. FEV_1 as a functional indicator of airway obstruction was correlated to B_{in}/A, B_{wt}/A, B_{wa}/B_{oa}, and MP count. There was a significant and positive association for B_{in}/A (p = 0.002), and a significant and negative association for B_{wt}/A, B_{wa}/B_{oa} and MP count (all p<0.0001). MP count was significantly (p=0.023) correlated to the presences of *Pseudomonas aeruginosa*, and a trend (p=0.06) was observed for NTM. Patients with ≥2 severe exacerbations showed a significant association with bronchial wall thickening (B_{wt}/A (p=0.02), B_{wa}/B_{oa} (p=0.03)) and MP count (p =0.04). For the association between aetiology and BA and MP metrics, we observed that the category post-infective showed a significant and negative association with B_{out}/A, B_{in}/A, and B_{wt}/A. For PCD, a significant and positive association was

Table 2. Multiple regression analysis for BA-ratios and mucus plugs metrics

		B_{out}/A			B_{in}/A			B_{wt}/A			B_{wa}/B_{na}			MP count			MP volume		
		Estimate	SE	P-value	Estimate	SE	P-value	Estimate	SE	P-value	Estimate	SE	P-value	Estimate	SE	P-value	Estimate	SE	P-value
model 1	**Age**	0.002	0.001	**0.002**	0.002	0.001	**0.005**	0.000	0.000	0.222	0.000	0.000	0.265	0.026	0.008	**0.002**	0.006	0.003	**0.014**
	Gender (Female)	0.056	0.024	**0.017**	0.036	0.022	0.094	0.016	0.007	**0.022**	0.005	0.008	0.562	0.309	0.261	0.237	0.015	0.081	0.852
	Length of disease to enrolment			0.117			**0.025**			**<0.0001**			**<0.0001**			**<0.0001**			**<0.0001**
	0 – 5 years	Ref			Ref			Ref			Ref			Ref			Ref		
	5 – 9 years	0.052	0.030	0.083	0.053	0.027	0.054	-0.001	0.009	0.919	-0.015	0.010	0.160	0.174	0.329	0.597	0.042	0.103	0.680
	10-14 years	0.051	0.037	0.169	0.047	0.034	0.168	0.007	0.011	0.513	-0.003	0.013	0.832	0.836	0.410	**0.042**	0.195	0.128	0.127
	15-20 years	0.093	0.047	**0.049**	0.059	0.043	0.172	0.031	0.014	**0.028**	0.015	0.016	0.358	1.768	0.521	**0.001**	0.512	0.163	**0.002**
	>20 years	0.046	0.031	0.147	0.021	0.029	0.458	0.023	0.010	**0.016**	0.011	0.011	0.317	0.549	0.348	0.115	0.184	0.109	0.090
	FEV_1, %pred	0.141	0.046	**0.002**	0.272	0.042	**<0.0001**	-0.125	0.014	**<0.0001**	-0.182	0.016	**<0.0001**	-3.124	0.513	**<0.0001**	-0.829	0.160	**<0.0001**
	Microbiology																		
	PsA isolation	-0.002	0.023	0.917	-0.002	0.021	0.912	0.000	0.007	0.993	0.000	0.008	0.972	0.589	0.259	**0.023**	0.143	0.081	0.077
	NTM isolation	-0.011	0.033	0.745	-0.004	0.030	0.885	-0.004	0.010	0.690	-0.003	0.011	0.823	0.685	0.363	0.060	0.189	0.113	0.096
	Smoking status			0.668			0.295			0.140			**0.014**			0.655			0.393
	Never	Ref			Ref			Ref			Ref			Ref			Ref		
	Ex	0.013	0.024	0.581	0.025	0.022	0.245	-0.013	0.007	0.062	-0.017	0.008	**0.038**	-0.100	0.262	0.702	-0.090	0.082	0.269
	Current	-0.020	0.048	0.671	-0.032	0.044	0.469	0.012	0.015	0.418	0.028	0.017	0.093	0.307	0.531	0.563	0.085	0.166	0.606
	Hospital Admissions			0.758			0.770			0.070			0.058			0.118			0.149
	0	Ref			Ref			Ref			Ref			Ref			Ref		
	1	0.026	0.032	0.414	0.026	0.029	0.369	-0.001	0.010	0.907	-0.009	0.011	0.392	0.135	0.352	0.703	0.030	0.110	0.784
	≥2	0.022	0.044	0.615	-0.005	0.041	0.897	0.031	0.013	**0.021**	0.034	0.015	**0.028**	1.024	0.491	**0.038**	0.299	0.153	0.052
	Aetiology			**0.006**			**0.006**			**<0.0001**			**<0.0001**			**0.027**			0.059
	Idiopathic	Ref			Ref			Ref			Ref			Ref			Ref		
	ABPA	0.025	0.054	0.646	0.016	0.049	0.745	0.010	0.016	0.549	0.000	0.019	0.989	-0.330	0.593	0.578	-0.102	0.185	0.580
	Asthma	-0.043	0.065	0.507	-0.034	0.059	0.572	-0.019	0.020	0.327	-0.020	0.023	0.374	-0.634	0.717	0.377	-0.221	0.224	0.323
	Primary/secondary immunodeficiency	-0.034	0.046	0.457	-0.041	0.042	0.321	0.000	0.014	0.991	0.015	0.016	0.341	0.606	0.504	0.229	0.266	0.157	0.091
	CTD / RA / IBD	-0.017	0.055	0.758	-0.012	0.051	0.818	-0.007	0.017	0.676	-0.002	0.019	0.908	-0.070	0.612	0.909	0.121	0.191	0.525
	COPD	-0.042	0.067	0.531	-0.031	0.061	0.611	-0.003	0.020	0.876	0.004	0.023	0.858	-0.942	0.740	0.204	-0.337	0.231	0.145
	NTM	0.040	0.059	0.494	0.054	0.054	0.313	-0.020	0.018	0.263	-0.033	0.020	0.101	0.248	0.648	0.703	0.072	0.202	0.720
	Other diseases	-0.051	0.041	0.210	-0.045	0.037	0.233	-0.003	0.012	0.804	0.010	0.014	0.483	0.119	0.452	0.792	0.107	0.141	0.448
	Post Infective	-0.125	0.031	**<0.0001**	-0.102	0.029	**<0.0001**	-0.025	0.010	**0.009**	0.012	0.011	0.261	-0.671	0.348	0.054	-0.171	0.109	0.116
	PCD	0.025	0.050	0.619	-0.020	0.046	0.665	0.042	0.015	**0.006**	0.035	0.018	**0.048**	1.158	0.558	**0.038**	0.314	0.174	0.072
	Co-diagnosis of Asthma and/or COPD	-0.035	0.025	0.173	-0.052	0.023	**0.027**	0.020	0.008	**0.010**	0.035	0.009	**<0.0001**	0.094	0.282	0.738	0.059	0.088	0.503
	Elevated blood eosinophil count	0.020	0.036	0.579	0.002	0.033	0.954	0.011	0.011	0.297	0.005	0.012	0.693	0.525	0.394	0.182	0.200	0.123	0.104

Table 2. Continued

		B_{out}/A			B_{in}/A			B_{wt}/A			B_{wa}/B_{oa}			MP count			MP volume		
		Estimate	SE	P-value	Estimate	SE	P-value	Estimate	SE	P-value	Estimate	SE	P-value	Estimate	SE	P-value	Estimate	SE	P-value
model 2	BSI	-0.001	0.003	0.728	-0.006	0.003	**0.033**	0.004	0.001	**<0.0001**	0.005	0.001	**<0.0001**	0.176	0.031	**<0.0001**	0.048	0.010	**<0.0001**
model 3	FACED	-0.010	0.008	0.231	-0.027	0.008	**<0.0001**	0.017	0.003	**<0.0001**	0.022	0.003	**<0.0001**	0.611	0.090	**<0.0001**	0.179	0.028	**<0.0001**

This table shows multivariable linear regression to study the associations between BA-ratios, mucus plugs outcomes and the following clinical parameters. Results are presented in multiple linear regression as Estimate, Standard Error and p-value. For categories we also performed F-test for overall effects and present only as p-value*. Only if F-test for overall effect for categories are significant the P-values are reported for multiple linear regression.

Reference value (Ref) where chosen for categories: for gender – female; for history of bronchiectasis - <5 years; for smoking status – never; for Blood eosinophil count – normal tested; for underlying aetiology – idiopathic.

A total of 562 patients (model 1) were analysed in the main multiple linear regression analysis. However, BSI (model 2, total of 598 patients) and FACED (model 3, total of 590 patients) were put into different models (without their components) to avoid co-linearity.

Model 1 (main model) consists of age, length of disease, gender, underlying aetiology, co-diagnosis of Asthma and/or COPD, smoking status, FEV_1 %predicted, PA infection, NTM infection, hospital admissions, and blood eosinophil count.

Model 2 consists of age, length of disease, gender, underlying aetiology, co-diagnosis of Asthma and/or COPD, smoking status, blood eosinophil count and BSI.

Model 3 consists of age, length of disease, gender, underlying aetiology, co-diagnosis of Asthma and/or COPD, NTM infection, smoking status, blood eosinophil count and FACED score.

SE= standard error. Ref = reference. B_{out}/A= bronchial outer dimeter divided by adjacent artery diameter. B_{in}/A= bronchial inner dimeter divided by adjacent artery diameter. B_{wt}/A= bronchial wall thickness divided by adjacent artery diameter. B_{wa}/B_{oa}= bronchial wall area divided by bronchial outer area. ABPA = Allergic bronchopulmonary aspergillosis; CTD = connective tissue disease; RA = rheumatoid arthritis; IBD = inflammatory bowel disease; COPD = chronic obstructive pulmonary disease; NTM = nontuberculous mycobacteria. FEV1 %predicted = Forced expiratory volume in 1 second. BSI = Bronchiectasis Severity Index. FACED = FEV_1, Age, Chronic colonization, Extent and Dyspnea score.

observed with B_{wt}/A, B_{wa}/B_{oa}, and MP count. A co-diagnosis of COPD and or asthma was associated with a lower B_{in}/A, and higher B_{wt}/A, and B_{wa}/B_{oa}. No significant associations were observed between BA-metrics and MP metrics and elevated eosinophil count. BSI and FACED scores were correlated to B_{in}/A, B_{wt}/A, B_{wa}/B_{ou}, MP count and volume.

Correlations between BEST-CT and BA and MP-metrics

We observed weak to moderate correlations between BEST-CT scores and BA-ratios, and moderate correlations between BEST-CT scores and MP metrics (Table 3). Specifically, for bronchial dilatation, the correlation between %TBE and B_{out}/A was 0.381 (95%CI, 0.286, 0.470). For bronchial wall thickening, the correlation between %TinF and B_{wt}/A was 0.405 (95%CI, 0.315, 0.483). Among the MP metrics, the correlations were higher, with MP count and volume showing correlations with %TMP of 0.65 (95%CI, 0.58, 0.72) and 0.61 (95%CI, 0.53, 0.68), respectively.

Table 3. Correlations between BEST-CT scores and BA and MP metrics

	%TBE	%TMP	%TInF
B_{out}/A	0.38 (0.29, 0.47)	-	-
B_{in}/A	0.26 (0.17, 0.36)	-	-
B_{wt}/A	-	0.40 (0.31, 0.48)	0.41 (0.32, 0.48)
B_{wa}/B_{oa}	-	0.24 (0.15, 0.34)	0.26 (0.17, 0.35)
MP count	-	0.65 (0.58, 0.72)	0.59 (0.51. 0.66)
MP volume	-	0.61 (0.53, 0.68)	0.56 (0.47, 0.63)

The correlation coefficients (with 95% confidence intervals) between BEST-CT scores and BA and MP metrics are presented for 364 patients. Note that BA-ratios are summarized as a median in segmental generation G1-G6 for each CT. BA= bronchus and artery. MP= mucus plug. TBE = Total bronchiectasis TMP = Total mucus plugging. TInF = Total of inflammatory CT-characteristics. Bout = diameter of bronchus outer edge; Bin= diameter of bronchus inner edge; A = diameter of artery; Bwt = bronchus wall thickness; Bwa/Boa = bronchial wall area/bronchial outer area. MP = mucus plug

Discussion

In this study, we analysed CT scans obtained in a large cohort of bronchiectasis patients from the EMBARC registry using fully automatic AI-based software to assess BA and MP metrics on chest CT scans. In addition, outcomes of the fully automatic analysis was compared to visual BEST-CT scores. Our findings demonstrate substantial heterogeneity in the structural lung abnormalities present in bronchiectasis patients, which is consistent with the diverse clinical presentations and pathophysiological mechanisms associated with this condition. Furthermore, the correlations of BA and

MP metrics on the one hand, with clinical characteristics and visual BEST-CT scores on the other, demonstrate the feasibility and relevance of the automatic analysis for phenotyping bronchiectasis disease patients and its potential value for bronchiectasis diseases registries such as EMBARC.

We identified significant associations of BA and MP metrics with patient demographics, clinical characteristics, and exacerbations. Older patients and those with a longer duration of disease exhibited more pronounced bronchial and mucus abnormalities, consistent with the often progressive nature of bronchiectasis. Chronic airway inflammation and recurrent infection likely drive these changes, resulting in cumulative structural lung damage and mucus retention. Notably, the significant association between MP count and the presence of *Pseudomonas aeruginosa* supports the detrimental role that this bacteria can play in bronchiectasis patients, something long recognised in people with cystic fibrosis bronchiectasis. This finding aligns with previous studies that demonstrated a correlation between *Pseudomonas aeruginosa* in patients with bronchiectasis and an increased risk of exacerbations, as well as more severe bronchiectasis and mucus plugging on chest CT scan [17, 27, 28, 35, 36]. Furthermore, In COPD, an association has been described between the number of mucus-occluded segments through visual scoring and all-cause mortality in 4483 COPDGene participants[37]. These findings were recently corroborated in all COPD participants using the same method employed in our study[38]. In the context of bronchiectasis, the presence of mucus plugs on chest CT could also signal increased airway inflammation, with increased mucus secretion and retention secondary to a bacterial or fungal infection, contributing to the symptoms and progression.

Another important point highlighted by our study is the significant association between mucus plugging, bronchial wall thickening, and the number of severe exacerbations requiring hospital admission. Increased bronchial wall thickness may reflect both active inflammation resulting in swelling of the mucosa and in mucus adhering to the bronchial wall contributing to the increased wall thickness measurements[39]. Mucus accumulation amplifies the vicious cycle of inflammation, infection, and exacerbations, driving structural lung damage. The significant association between wall thickness markers and mucus plugging and the number of exacerbations requiring hospital admission underscores the idea that this subgroup of bronchiectasis patients experiences higher disease activity and potentially greater clinical consequences[37]. Effective mucus clearance is a key component of bronchiectasis management plans[4]. While previous studies have suggested a key role for inflammation in bronchiectasis, our findings add radiological evidence for the contribution of mucus plugging, in a large number of patients reinforcing the importance of addressing both inflammation and mucus in treatment strategies [17, 40].

An essential aspect of diagnosing and managing patients with bronchiectasis is identifying the underlying aetiology and associated comorbidities. An important finding of our study is the observation that different underlying aetiologies were found to associate with some, but not all, BA and MP metrics. For example, patients with PCD showed more inflammatory CT features, such as mucus plugging and bronchial wall thickening. These results are consistent with other studies, which also suggest that inflammation plays an important role in PCD [17, 41]. These findings suggest that PCD patients may benefit from more intensive mucus clearance, anti-inflammatory, and/or antibiotic treatments. In contrast, post-infective bronchiectasis significantly associated with lower mucus plugs metrics, which is consistent with our previous findings [17]. This, supports the concept of "dried-up" bronchiectasis, which formed during a historical episode of inflammation and bronchial damage, but with less active ongoing inflammatory disease. Moreover, there was significantly less bronchiectasis in post-infective cases compared to other aetiologies, which is also consistent with our previous findings. This makes sense, as post-infectious bronchiectasis often involves only a single segment or lobe, unlike diffuse bronchial damage observed in other systemic aetiologies such as immune deficiencies or PCD. Additionally, bronchiectasis patients with overlapping conditions such as a co-diagnosis of asthma and/or COPD had significantly lesser extent of bronchial dilatation compared to patients without a co-diagnosis of asthma and/or COPD, but interestingly increased airway wall thickness markers. As described before, this is important in light of research on BE and COPD and/or asthma overlap syndromes. It suggest that the symptoms of these patients could arise predominantly from their small airway disease rather than in the medium-sized and larger airways as detected on chest CTs. However, the significantly higher bronchial wall thickening in bronchiectasis patients with a co-diagnosis of asthma and/or COPD compared to patients without this co-diagnosis suggests that chronic bronchial inflammation does contribute to their symptoms.

Although we found significant correlations between all BAs and MP metrics with lung function, the observed positive correlation between B_{in}/A and FEV_1 warrants further discussion. FEV_1, as a measure of airflow, is typically associated with the internal diameter of the airways. Our study found a positive correlation between B_{in}/A and FEV_1, indicating that a relatively wider bronchial inner diameter to adjacent arterial diameter is associated with higher airflow and better lung function. We find this a logical association and it underlines our plea to define pathological bronchial dilatation on the basis of the outer diameter of the bronchus, rather than the inner diameter, which is still often considered [7] . Conversely, higher B_{wt}/A and B_{wa}/B_{oa}, indicative of bronchial wall thickening, likely correspond with a diminished bronchial lumen, as well as reflect more significant airway remodeling or chronic inflammation, correlating with lower FEV_1 values [42].

The BA and MP metrics broadly align with the BEST-CT scoring method, demonstrating their potential as objective tools for evaluating BA-dimensions and mucus plugs in bronchiectasis disease patients. BA and MP metrics correlated to comparable outcomes for the BEST-CT and can be used to quantify bronchial dimensions with great precision in bronchiectasis patients. It has previously been shown that bronchial dilatation, as measured by BA dimensions, correlates with similar outcomes in the BEST-CT scoring method, particularly at higher cut-off values [21]. Especially the assessment of bronchi showing mild bronchial dilatation (i.e. B_{out}/A between 1.1 and 1.5) of all visible BA-pairs in daily practice is not feasible as it is too time-consuming and is considered difficult and poorly reproducible between experts [17, 32]. In the current study, 34% of all BA-pairs measured fell in this 1.1 to 1.5 category, while 39% fell in the severe category of >1.5 as determined by B_{out}/A. Future clinical application of BA-analysis in bronchiectasis patients could be used to report the percentage of mild and severely enlarged airways and provide longitudinal follow-up to monitor disease progression.

Though the BA-analysis we used captures key elements related to airway disease, we did not include AI based algorithms to capture parenchymal changes such as emphysema for this retrospective analysis. This would have been relevant especially for the 12% of patients who also had a co-diagnosis of COPD. However, for the correct diagnosis of emphysema volume standardization is of key importance. Furthermore, for the reliable diagnosis of emphysema, an expiratory scan is considered important[43]. Unfortunately, these were not routinely collected in most patients for which reasons we did not include this analysis in our study. Furthermore, it should be investigated whether it is clinically relevant to quantify other parenchymal changes such as consolidations, fibrosis or ground-glass opacities. Given the important contribution of airway related structural changes and the substantial time requirements of the BEST-CT method, the automatic analysis of BA and MP metrics is well-positioned as starting point for the quantification of key structural changes in bronchiectasis patients in registry studies and in the future also for daily clinical care.

While our study benefits from a large sample size and objective and reproducible measurements, some limitations should be considered. The cross-sectional design of this study limits our ability to infer causal relationships between structural changes, clinical parameters, and outcomes. Furthermore longitudinal studies are needed to elucidate how these structural abnormalities evolve over time and their potential role in predicting disease progression or response to therapy. Another limitation of this study is the lack of volume optimisation and protocol standardization; however, addressing this is expected to further improve the sensitivity and accuracy of our findings.

Quantitative CT imaging, as demonstrated in this study, provides detailed, reproducible data on bronchial measurements and mucus plugs, linking structural changes to clinical outcomes such as airflow obstruction and disease severity. These metrics may support risk stratification and facilitate the identification of distinct inflammatory phenotypes, enabling tailored treatment approaches for subgroups of bronchiectasis disease patients. Furthermore, these metrics will enable clinicians to reliably assess subtle structural changes, particularly in the context of longitudinal disease monitoring, providing much needed non-invasive biomarkers [5]. We demonstrated that the fully automated analysis provides similar outcome measures compared to a semi-automated analysis technique, but with much greater precision and efficiency. This made it feasible to fully automatically analyse the CTs of a large cohorts of patients such as the EMBARC registry, which will be extremely important to advance our understanding of bronchiectasis disease.

In conclusion, this study highlights the utility of AI-based software in evaluating bronchiectasis-related lung abnormalities and underscores the complex relationships between structural changes, clinical characteristics, and outcomes in bronchiectasis patients. The observed associations between BA and MP metrics, and clinical factors suggest that these imaging-derived biomarkers could provide valuable insights into disease severity, progression, and management.

References

1. Chalmers, J.D., et al., *Bronchiectasis.* Nat Rev Dis Primers, 2018. **4**(1): p. 45.
2. Chandrasekaran, R., et al., *Geographic variation in the aetiology, epidemiology and microbiology of bronchiectasis.* BMC Pulm Med, 2018. **18**(1): p. 83.
3. McShane, P.J., et al., *Non-cystic fibrosis bronchiectasis.* Am J Respir Crit Care Med, 2013. **188**(6): p. 647-56.
4. Polverino, E., et al., *European Respiratory Society guidelines for the management of adult bronchiectasis.* European Respiratory Journal, 2017. **50**(3): p. 1700629.
5. Johnson, E., M.B. Long, and J.D. Chalmers, *Biomarkers in bronchiectasis.* European Respiratory Review, 2024. **33**(173): p. 230234.
6. Meerburg, J.J., et al., *Diagnosis and quantification of bronchiectasis using computed tomography or magnetic resonance imaging: A systematic review.* Respir Med, 2020. **170**: p. 105954.
7. Tiddens, H., et al., *The radiological diagnosis of bronchiectasis: what's in a name?* Eur Respir Rev, 2020. **29**(156).
8. Hansell, D.M., et al., *Fleischner Society: glossary of terms for thoracic imaging.* Radiology, 2008. **246**(3): p. 697-722.
9. Bankier, A.A., et al., *Fleischner Society: Glossary of Terms for Thoracic Imaging.* Radiology, 2024. **310**(2): p. e232558.
10. Jennifer J. Meerburg, A.G.-U., Olivier Dragt, Eleni-Rosalina Andrinopoulou, Mariette, P.C. Kemner van de Corput, Pierluigi Ciet, Gerhild Angyalosi, J. Stuart Elborgn, James D. Chalmers, Michael Tunney, Merleen de Bruine, Harm A.W.M. Tiddens, on behalve of the iABC study group, *Quantitative chest computed tomography scoring technique for bronchiectasis (BEST-CT).* Submitted.
11. Rogers, W., et al., *Radiomics: from qualitative to quantitative imaging.* Br J Radiol, 2020. **93**(1108): p. 20190948.
12. Bhalla, A.S., et al., *Imaging protocols for CT chest: A recommendation.* Indian J Radiol Imaging, 2019. **29**(3): p. 236-246.
13. Long, M.B., et al., *Rethinking bronchiectasis as an inflammatory disease.* Lancet Respir Med, 2024. **12**(11): p. 901-914.
14. Bhalla, M., et al., *Cystic fibrosis: scoring system with thin-section CT.* Radiology, 1991. **179**(3): p. 783-8.
15. Reiff, D.B., et al., *CT findings in bronchiectasis: limited value in distinguishing between idiopathic and specific types.* AJR Am J Roentgenol, 1995. **165**(2): p. 261-7.
16. Brody, A.S., et al., *Reproducibility of a scoring system for computed tomography scanning in cystic fibrosis.* J Thorac Imaging, 2006. **21**(1): p. 14-21.
17. Pieters, A.L.P., et al., *Structural Lung Disease and Clinical Phenotype in Bronchiectasis Patients: The EMBARC CT Study.* Am J Respir Crit Care Med, 2024. **210**(1): p. 87-96.
18. Meerburg, J.J., et al., *Analysis of Granulomatous Lymphocytic Interstitial Lung Disease Using Two Scoring Systems for Computed Tomography Scans-A Retrospective Cohort Study.* Front Immunol, 2020. **11**: p. 589148.
19. Kuo, W., et al., *Objective airway artery dimensions compared to CT scoring methods assessing structural cystic fibrosis lung disease.* J Cyst Fibros, 2017. **16**(1): p. 116-123.
20. Charbonnier, J.P., et al., *Airway wall thickening on CT: Relation to smoking status and severity of COPD.* Respir Med, 2019. **146**: p. 36-41.
21. Pieters, A.L.P., et al., *Automated method of bronchus and artery dimensions of an adult bronchiectasis population.* ERJ Open Research, 2024: p. 00231-2024.
22. Pieters, A., et al., *The spectrum of structural lung changes in bronchiectasis: Analysis of 524 EMBARC CTs.* European Respiratory Journal, 2023. **62**(suppl 67): p. PA1074.

23. Chalmers, J.D., et al., *The EMBARC European Bronchiectasis Registry: protocol for an international observational study.* ERJ Open Res, 2016. **2**(1).
24. Chalmers, J.D., et al., *Bronchiectasis in Europe: data on disease characteristics from the European Bronchiectasis registry (EMBARC).* Lancet Respir Med, 2023. **11**(7): p. 637-649.
25. Griffith, D.E., et al., *An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases.* Am J Respir Crit Care Med, 2007. **175**(4): p. 367-416.
26. Zhou, Y., et al., *Global prevalence of non-tuberculous mycobacteria in adults with non-cystic fibrosis bronchiectasis 2006-2021: a systematic review and meta-analysis.* BMJ Open, 2022. **12**(8): p. e055672.
27. Chalmers, J.D., et al., *The bronchiectasis severity index. An international derivation and validation study.* Am J Respir Crit Care Med, 2014. **189**(5): p. 576-85.
28. Martínez-García, M., et al., *Multidimensional approach to non-cystic fibrosis bronchiectasis: the FACED score.* Eur Respir J, 2014. **43**(5): p. 1357-67.
29. Shoemark, A., et al., *Characterization of Eosinophilic Bronchiectasis: A European Multicohort Study.* Am J Respir Crit Care Med, 2022. **205**(8): p. 894-902.
30. Lutey, B.A., et al., *Accurate measurement of small airways on low-dose thoracic CT scans in smokers.* Chest, 2013. **143**(5): p. 1321-1329.
31. Aliberti, S., 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, 2022. **10**(3): p. 298-306.
32. Lv, Q., et al., *Automatic analysis of bronchus-artery dimensions to diagnose and monitor airways disease in cystic fibrosis.* Thorax, 2023.
33. Kokonendji, C.C., W.H. Bonat, and R. Abid, *Tweedie regression models and its geometric sums for (semi-)continuous data.* WIREs Computational Statistics, 2021. **13**(1): p. e1496.
34. Koo, T.K. and M.Y. Li, *A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research.* J Chiropr Med, 2016. **15**(2): p. 155-63.
35. Finch, S., et al., *A Comprehensive Analysis of the Impact of Pseudomonas aeruginosa Colonization on Prognosis in Adult Bronchiectasis.* Ann Am Thorac Soc, 2015. **12**(11): p. 1602-11.
36. Miszkiel, K.A., et al., *Effects of airway infection by Pseudomonas aeruginosa: a computed tomographic study.* Thorax, 1997. **52**(3): p. 260-4.
37. Diaz, A.A., et al., *Airway-Occluding Mucus Plugs and Mortality in Patients With Chronic Obstructive Pulmonary Disease.* Jama, 2023. **329**(21): p. 1832-1839.
38. van der Veer, T., et al., *Association between automatic AI-based quantification of airway-occlusive mucus plugs and all-cause mortality in patients with COPD.* Thorax, 2024: p. thorax-2024-221928.
39. Chen, Y., et al., *Automatic bronchus and artery analysis on chest computed tomography to evaluate the effect of inhaled hypertonic saline in children aged 3-6 years with cystic fibrosis in a randomized clinical trial.* J Cyst Fibros, 2023.
40. Keir, H.R., et al., *Neutrophil extracellular traps, disease severity, and antibiotic response in bronchiectasis: an international, observational, multicohort study.* Lancet Respir Med, 2021. **9**(8): p. 873-884.
41. Rademacher, J., et al., *The Primary Ciliary Dyskinesia Computed Tomography Score in Adults with Bronchiectasis: A Derivation und Validation Study.* Respiration, 2021. **100**(6): p. 499-509.
42. Mohamed Hoesein, F.A.A., et al., *Airway wall thickness associated with forced expiratory volume in 1 second decline and development of airflow limitation.* European Respiratory Journal, 2015. **45**(3): p. 644-651.
43. Müller, N.L., et al., *"Density mask". An objective method to quantitate emphysema using computed tomography.* Chest, 1988. **94**(4): p. 782-7.

Appendix

Table S1. CT scanner characteristics

CT scanner manufacturer	CT scanner type	Kernels	Slice thickness (mm)
Canon Medical Systems	Aquilion Lightning	LUNG	1
	Aquiliion Prime SP	LUNG	1
GE Medical systems	Brightspeed	Boneplus	1.25
		CHST	1.25
		Lung	1.25
		Soft	0.625, 1.25
		Standard	1.25
	Brightspeed QX/i	Boneplus	1.25
	Brightspeed S	Standard	1.25
	Discovery CT750 HD	Boneplus	1.25
		HD lung	1.25
		Standard	1.25
	Discovery MI	Chest	1.25
		Lung	1.25
	Lightspeed Pro 32	Lung	1.25
		Standard	1.25
	LightSpeed VTC	Bone	1.25
		Chst	0.625, 1.25
		Lung	1.25
		Soft	0.625, 1.25
		Standard	0.625, 1.25
	Optima CT520 Series	Standard	1.25
	Optima CT540	Boneplus	1.25
		Lung	1.25
		Standard	1.25
	Optima CT660	Boneplus	1.25
		Chst	1.25
		Standard	1.25
	Revolution CT	Standard	0.625, 1.25
	Revolution EVO	Boneplus	1.25
		Chst	1.25
		Lung	0.625, 1.25
		Standard	0.625, 1,25
	Revolution HD	Standard	0.625, 1.25
Hitachi, Ltd.	FCT Speedia	21	1.25
Philips	Access CT	Lung B	1
	Brilliance 16	L	1
		YD	1
	Brilliance 16 P	B	1
	Brilliance 64	B	1, 1.5
	Briliance 64	B	1, 1.5
		C	1, 1.5
		L	0.9, 1

Table S1. Continued

CT scanner manufacturer	CT scanner type	Kernels	Slice thickness (mm)
		YA	1
		YB	1
		YC	1
	Briliance16	L	1
	Gemini LXL	L	1
	iCT 128	YC	1
	iCT 256	A	1.25
		B	0.9
		CB	0.9
		L	1
		YA	0.8, 0.9, 1.4
		YB	1
		YC	1
	iCT SP	YB	1
	Ingenuity Core	B	1.5
		YC	1
	Ingenuity Core 128	B	1, 1.5
	Inguinity CT	B	1, 1.5
Siemens	Biography128	B26f	1
		B70f	1
		B75f	
	Biography40	B70f	1
	Definition AS+	B31f	1.5
		B70f	1
		B70s	1
	Emotion 16	B70s	1
		B80s	1
	Emotion 16 (2007)	B31s	1.5
		B80s	1
	Emotion 16 (2010)	B70s	1
	Emotion 6	B70s	1
	Perspective	I30s\2	1.5
		I50s\1	1
	SafeCT	B90s	1.5
	Sensation 16	B31f	1
		B70f	1
		B80s	1
	Sensation 40	B31f	1
		B30f	1
		B40f	1
		B41f	1
		B70f	1, 1.5
	Sensation Cardiac	B70f	1
		B70s	1
	Sensation Cardiac 64	B30f	1.5
	SOMATOM Definition	B20f	0.75, 1, 1.5
		B25f	1

Table S1. Continued

CT scanner manufacturer	CT scanner type	Kernels	Slice thickness (mm)
		B31f	0.75, 1
		B40f	0.75
		B70f	1
		B80f	1, 1.5
		I70f\3	1
	SOMATOM Definition AS	B10f	1.5
		B30f	1, 1.5
		B31f	0.75, 1
		B60f	1.5
		B75f	0.75
		I30f\3	1
		131f\3	1
		I70f\3	1
	SOMATOM Definition AS+	B20f	1
		B26f	1
		B30f	1
		B31f	1
		B50f	1
		B70f	0.75, 1, 1.5
		B75f	1
		I30f\1	1
		I30f\2	1
		I30f\3	1
		I31f\3	1
		I70f\3	1
	SOMATOM Definition Edge	B30f	1
		B70f	1
		I26f\3	1
		I30f\3	1
		I70f\3	1
	SOMATOM Definition Flash	B26f	1
		B30f	1
		B31f	1
		B50f	1
		B70f	1, 1.5
		B80f	1
		I26f\3	1
		I30f\3	1
		I70f\1	1
		I70\3	1, 1.5
		I70h\3	1
	SOMATOM Drive	I70f\3	1
	SOMATOM Force	Bl57d\3	1
		BL64d\3	1
		Br36d\3	1
		Br40d\1	1
		Br40d\3	1

Table S1. Continued

CT scanner manufacturer	CT scanner type	Kernels	Slice thickness (mm)
		Bv36d\3	1
		Bv40d\3	1
	SOMATOM go.TOP	Br64f\3	1
	SOMATOM go.Up	Br60f\3	1
	SOMATOM Perspective	I80s	1
	SOMATOM Scope	I41s	1.5
	Symbia T16	B41s	1
TOSHIBA	Activion16	FC07	1
	Alexion	FC08	1
	Acquilion	FC02	1
		FC03	1
		FC07	1
		FC08	1
		FC10	1
		FC18	1
		FC52	1
		FC55	1
		FC56	1
	Aquilion Lightning	FC07	1
	Aquilion ONE	FC01	0.5
		FC08	0.5
		FC09	1
		FC55	1
	Aquilion Prime SP	FC43	1
	Asteion	FC17	1
	Astelion	FC07	1

Table S2. Intraclass correlation coefficients of BEST-CT

Scores	Intra	Inter
%ATCON	0.98	0.93
%BEMP	0.99	0.29
%BEwMP	0.99	0.75
%TBE	0.99	0.93
%AWT	0.95	0.69
%MP	0.91	0.63
%GGO	0.19	0.60
%BUL	0.99	0.99
%HA	0.89	0.30
%HP	0.97	0.83

This table presents intra- and inter-observer agreement for the BronchiEctasis Scoring Technique for Computed Tomography (BEST-CT) expressed in intra-class correlation coefficients (ICC).

Certification was obtained by completion of standardized training modules (CF-CT, PRAGMA-CF and BEST-CT). The observer who scored all CT scans was a radiology resident with subspecialty training in thoracic radiology (AvB). The second observer for the inter-observer reliability was a certified LungAnalysis laboratory staff (M.B.). To assess intra-observer variability of the BEST-CT scoring method the main observer rescored 28 randomly selected CTs, one month after completion.

ATCON = Atelectasis and/or consolidation; BEMP = Bronchiectasis with mucus plugging. BEwMP = Bronchiectasis without mucus plugging; TBE = total bronchiectasis (BEMP + BEwMP). AWT = airway wall thickening. MP = Mucus plugging; GGO = Ground-glass opacities. BUL = bullae. A = airways. P = parenchyma.

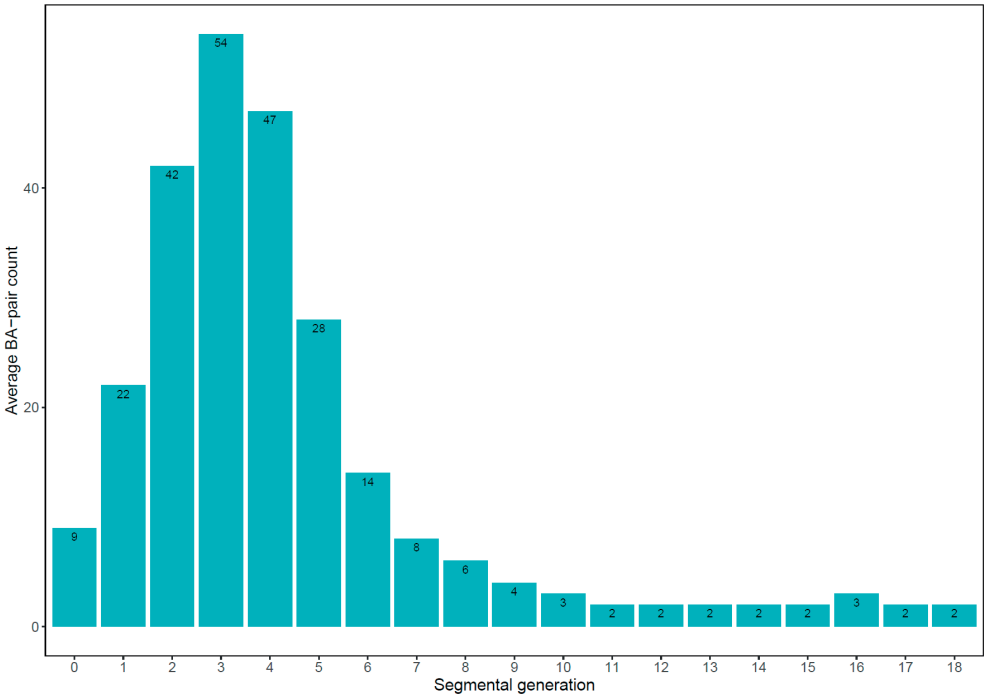

Figure S1. Average number of BA-pairs per segmental generation

BA= bronchus and artery. Note that the highest number of BA-pairs in both treatment groups could be detected in segmental generation G3.

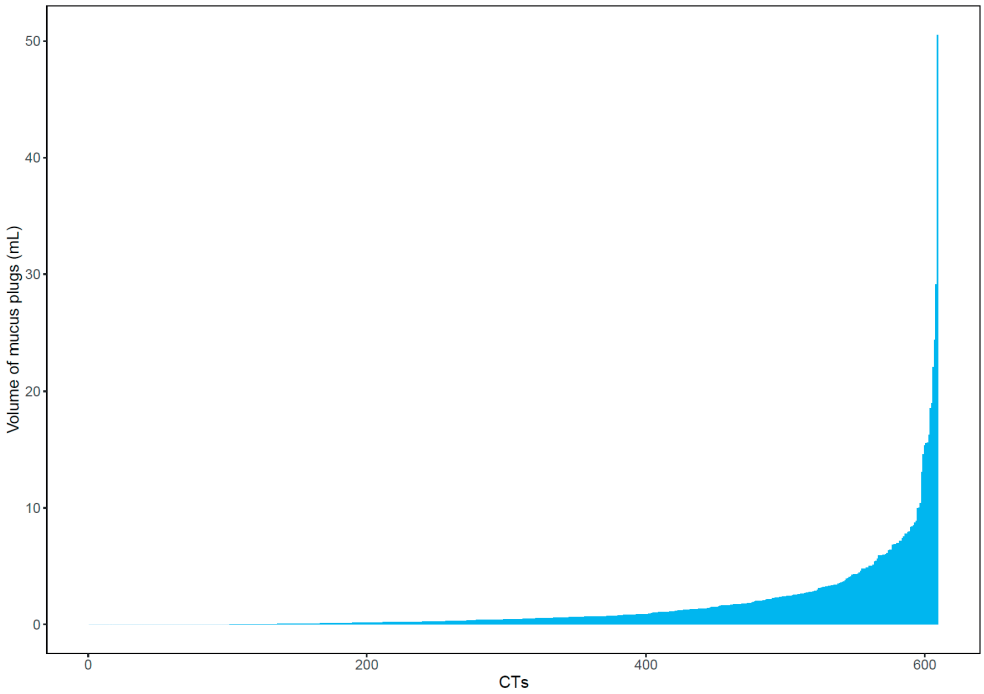

Figure S2. Distribution of mucus plug volume

This figure shows the volume of mucus plugs detected on the chest CT. There is a wide range between 0 and 50.51mL per CT. MP= mucus plug.

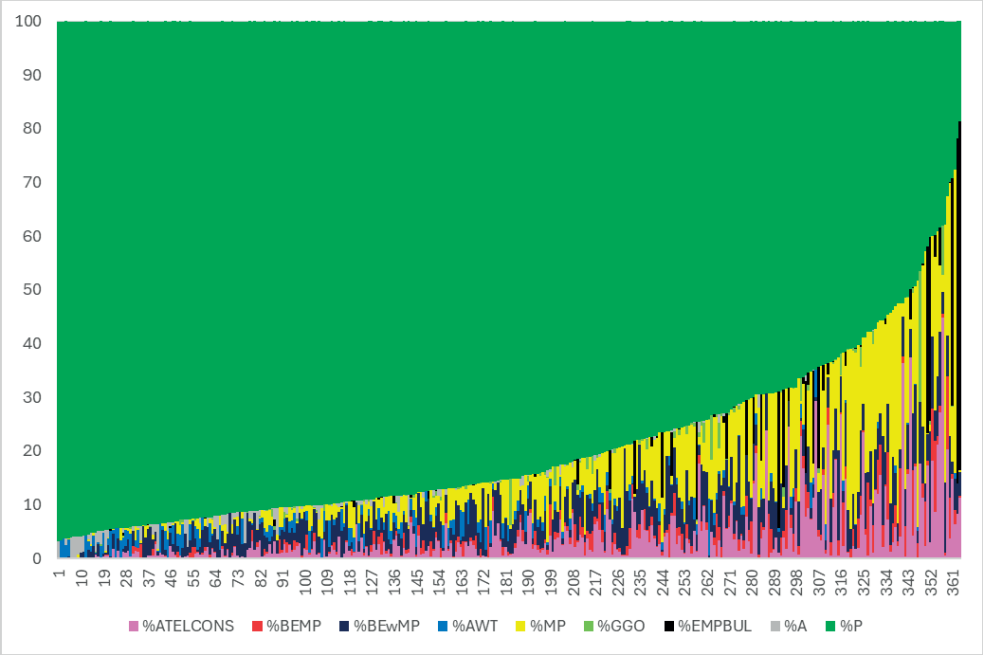

Figure S3. Visual distribution of the EMBARC population (n=364).

This stacked bar chart shows the results of BronchiEctasis Scoring Technique for Computed Tomography (BEST-CT) scoring of 364 chest computed tomography (CT) scans which were included for the automatic analysis. Each stacked bar represents the analysis results of one CT scan. Component scores are expressed as percentage of total lung volume and add up to 100% on the Y-axis. On the X-axis patients are represented (n = 364).

Subscores in the order by which they are scored. ATCON = Atelectasis and/or consolidation; BEMP = Bronchiectasis with mucus plugging. BEwMP = Bronchiectasis without mucus plugging; AWT = airway wall thickening. MP = Mucus plugging; GGO = Ground-glass opacities. BUL = bullae. A = Airways. P = Parenchyma). Patients are sorted based on the total disease score (%DIS) = %ATCO + %TBE + %AWT + %MP + %GGO + %BUL.

Chapter 5

Automated Computed Tomographic Analysis of Bronchial Thickness and Mucus Plugs in Bronchiectasis with Asthma

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Abstract

Introduction: Bronchiectasis disease is characterised by cough, sputum, and exacerbations, with chest CT typically showing bronchial wall thickening, and mucus plugging in addition to bronchial dilation. Asthma is a common comorbidity and associated with increased, eosinophilic, airway inflammation. Automated measurements of bronchial wall thickening and mucus plugs may serve as biomarkers for inflammation and associated with clinical characteristics such as spirometry, blood eosinophil count, and disease severity in patients with bronchiectasis and asthma co-diagnosis.

Methods: In a cross-sectional retrospective cohort of 64 patients with bronchiectasis disease and asthma, we applied automated image analysis to assess bronchial dimensions and mucus plug metrics on chest CT scans. These metrics were correlated with spirometry,blood eosinophil counts as well as Bronchiectasis Severity Index (BSI) and FEV_1, Age, Colonization, Extension and Dyspnea (FACED) scores using correlations and multiple regression analyses.

Results: In 63 patients, bronchial wall thickness and mucus plugs were quantified.] Negative correlations were observed between bronchial wall thickness markers and spirometry (B_{wt}/A and FEV_1, r=-0.37; FEV_1/FVC, r=-0.30). Mucus plugs correlated negatively with spirometry and positively with BSI and FACED scores (no. of mucus plugs and BSI, r=0.45). Correlations with blood eosinophil counts were very weak. In multiple regression analyses, independent associations were observed for FEV_1, *Pseudomonas aeruginosa* and frequent exacerbations.

Conclusion: This study identified key relationships between automated measurements of bronchial wall thickness and mucus plugs with clinical characteristics, highlighting their potential as imaging biomarkers to enhance phenotyping, improve risk assessment, and facilitate tailored treatment strategies in bronchiectasis.

Introduction

Bronchiectasis disease is characterised by cough, sputum production, and recurrent exacerbations, together with the radiological appearance of abnormal dilatation of bronchi.[1] Chronic airway inflammation is an important driving factor for clinical symptoms and outcomes in these patients, with airway remodeling and altered airway structure as consequences of the inflammatory process.[2, 3] On chest computed tomography (CT), changes such as wall thickening and mucus plugging are indicative of ongoing inflammation and are highly prevalent in bronchiectasis disease patients.[4] In the clinic, these markers have been linked to exacerbations and can potentially be used to differentiate between inflammatory 'active' or 'inactive' phenotypes.[5]

A promising development is the emergence of artificial intelligence (AI) based automated tools for the precise quantification of airway dimensions on chest CT scans, which may be used for *in vivo* monitoring of disease activity and progression. Bronchial wall thickening can reduce the airway inner diameters (lumen) and decrease airway compliance, which are key determinants of airflow obstruction. Therefore, airway dimensions are an important link between radiology and lung function. Traditionally, visual radiological evaluation of CT scans in bronchiectasis disease prioritises those airways labelled as bronchiectasis, which have already undergone permanent significant widening and thickening. A more sensitive automatic assessment of bronchial wall thickening and mucus plugging could detect the consequences of airway inflammation earlier, potentially allowing for earlier anti-inflammatory interventions before irreversible widening occurs.[3]

Automated assessment of bronchus-artery (BA) pair dimensions has been shown to be sensitive for detecting bronchial wall thickening and bronchial widening in cystic fibrosis (CF),[6, 7], non-CF bronchiectasis, and COPD . [8, 9] and paediatric asthma. [10] Automated assessment of mucus plugs has recently also been applied on large real-life cohorts of COPD patients as well as non-CF bronchiectasis and cystic fibrosis. [11-13]

Additional developments in bronchiectasis disease have focused on identifying inflammatory endotypes. While neutrophilic inflammation is most prevalent, eosinophils have also demonstrated elastolytic capacity and the secretion of substances that can damage the bronchial wall such as eosinophil cationic protein and metalloproteases.[14] In addition, eosinophils have been implicated in the formation of mucus plugs.[15] An eosinophilic endotype was identified in 22.6% of a large cohort of bronchiectasis patients, based on blood eosinophil counts of $\geq 0.3*10^9$/L.[16]

As known, particularly in severe asthma around 80% of patients have an eosinophilic endotype.[17] Bronchiectasis disease has a high co-occurrence of asthma, as well as COPD, sometimes also called overlap syndromes, which have been associated with higher inflammation and worse outcomes. [18-21] Interestingly, it was shown in the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) cohort that 31% of bronchiectasis disease patients have a co-diagnosis of asthma. [22] Inversely, radiological bronchiectasis is reported as a common comorbidity in asthma, with a significantly higher prevalence in severe eosinophilic asthma compared with mild asthma. [23] Asthma is characterised by bronchial hyperreactivity and chronic inflammation of both the larger and small airways. [24]

To investigate the relationship between radiological markers of bronchial wall thickening and mucus plug formation with clinical characteristics such as lung function and blood eosinophil counts, we applied automated image analysis to chest CTs of a cross-sectional cohort of bronchiectasis disease patients with co-diagnosed asthma. By utilizing CT features as biomarkers, the goal is to better understand and phenotype these patients, and tailor anti-eosinophilic and mucolytic treatments to the patients most likely to benefit.

Hypothesis: Bronchial wall thickening and mucus plugging, as assessed by CT and automated image analysis, are related to clinical characteristics, lung function, and blood eosinophil counts in patients with bronchiectasis disease and an asthma co-diagnosis.

Research questions:
1. What is the relationship between bronchial wall thickness and mucus plugs (as measured by automated tools on chest CT scans) with spirometry?
2. What is the relationship between bronchial wall thickness and mucus plugs with blood eosinophil counts?
3. How are specific clinical factors (e.g. age, dyspnoea, *Pseudomonas* colonisation, FACED/BSI-scores, and exacerbation frequency) associated with bronchial wall thickness and mucus plugs?

Methods

The BASIIS (Bronchiectasis & Asthma Identification and Inflammatory phenotyping Study) is a retrospective cross-sectional cohort using clinical data from 2018-2021 from the Erasmus MC University Medical Centre (Rotterdam, NL) bronchiectasis clinic. Inclusion criteria: ≥18 years, bronchiectasis (based on ICD-10 J47 in July 2020),

and a diagnosis of asthma in the clinical notes. After screening 255 bronchiectasis patients, 78 with asthma co-diagnosis were selected. Exclusion criteria: no mention of bronchiectasis in the chest CT report, unsuitable chest CT scan (>5 years old, slice thickness >1.5mm, or slice gaps), negative bronchial provocation test, and incomplete records. After review, 64 patients were included in this study. See Figure 1. Patient data were collected and coded for pseudo-anonymity after institutional review board approval (MEC-2020-0061).

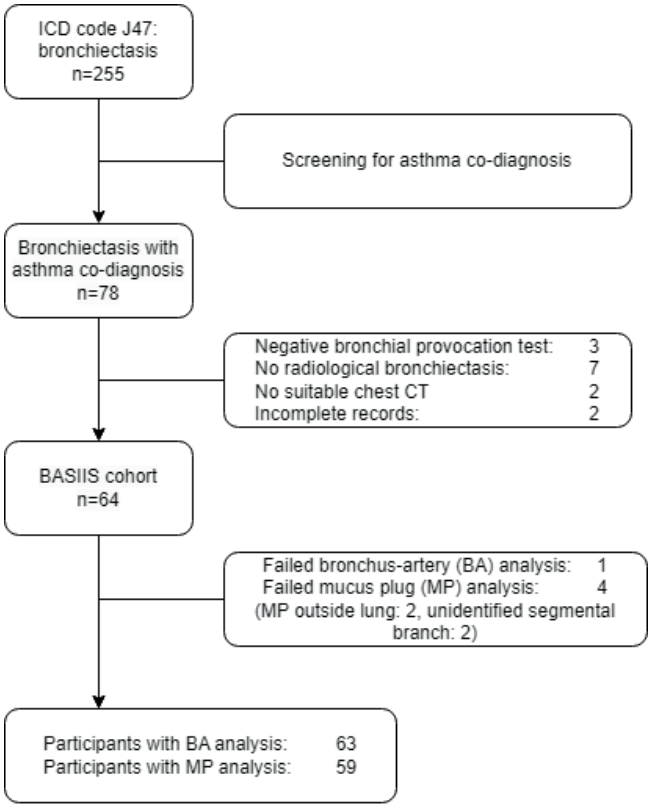


Figure 1. Inclusions flowchart

This figure shows the number of participants and reasons for exclusion. BA: bronchial artery analysis; MP: mucus plug analysis.

Data collection

Data were collected by the first author using the OpenClinica® electronic data capture platform (OpenClinica, LLC, Waltham USA). Spirometry followed ATS/ERS standards.[25] Height, weight and body mass index (BMI), smoking history, number of exacerbations and hospitalisations, modified medical research council (mMRC)

dyspnoea score, and medication use were derived from clinical records and prescription data. Laboratory results (blood eosinophil counts) were collected from digital patient records both closest to the CT scan date and if the patient had historical eosinophil measurements ≥$0.3*10^9$/L (yes/no). Bronchiectasis aetiology was determined by the treating pulmonologist after a workup conducted according to Dutch bronchiectasis guidelines.[26] Bacterial colonisation status was retrieved from sputum culture results. All extracted data were coded to ensure blinding. Missing data in the records were marked as missing in the database.

FACED and BSI

We assessed bronchiectasis severity using the FACED and BSI (Bronchiectasis Severity Index) scores. The FACED score combines FEV_1 (% predicted), age, colonisation by *Pseudomonas aeruginosa*, radiological extent of bronchiectasis, and mMRC dyspnoea scale, classifying patients into three categories of mortality risk: mild (0-2 points), moderate (3-4 points), and severe (5-7 points).[27] The BSI includes the additional variables of BMI, number of hospitalisations and exacerbations in the past year, and bacterial colonisation status, to predict hospitalisation and mortality rates. BSI categories: mild (0-4 points), moderate (5-8 points), and severe (≥9 points).[28]

Automated image analysis

Chest CT scans of the participants were retrieved from the hospital radiology system and pseudo-anonymized. The scans underwent preprocessing to identify the optimal inspiratory CT scan reconstruction for each participant based on following criteria: a minimum of 150 scan slices, slice thickness 1.5 mm or less, and no slice gap. The selected CT scans were then further analysed to determine BA ratios and the presence of mucus plugs using the fully automated AI-based software LungQ-BA v.2.0.1. and LungQ-MP v.3.0.1. (Thirona B.V., Nijmegen, the Netherlands).

LungQ-BA algorithm steps: 1. Bronchial tree segmentation; 2. Identification of detected bronchial branches; 3. Matching the adjacent artery for each detected bronchial branch (BA pairs); 4. Identification of the generation (G) number for each BA pair starting from the segmental bronchi (G_0); 5. Computation of BA dimensions: B_{in}, B_{wt}, B_{wa}, B_{oa}, and A; 6. Computation of BA ratios: B_{in}/A, B_{wt}/A, and B_{wa}/B_{oa}. See also Figure 2. Airway measurements are performed for airways proximal to an occluding mucus plug, so that dimensions reflect unobstructed bronchi.

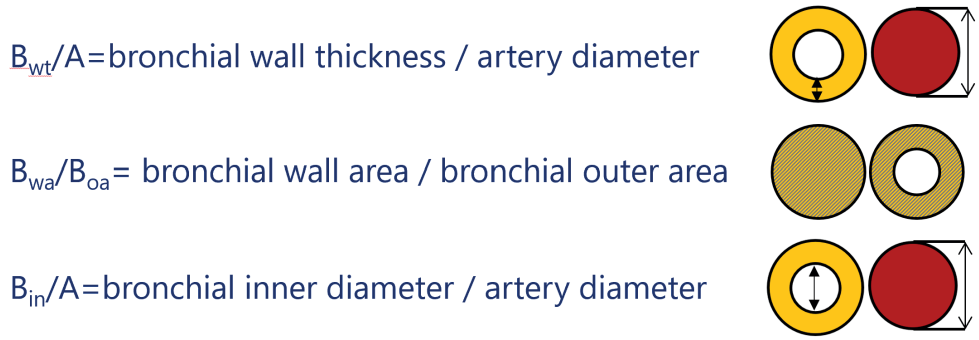


Figure 2. Bronchial Artery (BA)-measures.

This figure shows the bronchial and arterial dimensions and ratios as automatically measured by LungQ-BA. Bwt: bronchial wall thickness; Bwa: bronchial wall area; Boa: bronchial outer area; Bin: bronchial inner diameter; A: accompanying artery diameter.

Also, LungQ determines Pi10, a computed measure that represents the square root of the wall area of a hypothetical airway with an internal perimeter of 10 mm.[29]

As a measure of bronchial lumen, we used B_{in}/A. As a measure of wall thickness, we used B_{wt}/A and B_{wa}/B_{oa}. B_{wa}/B_{oa} is independent of arterial diameter, which may be altered by pathological changes in the pulmonary vasculature.

BA dimension results are presented from sub-segmental level onward ($G_{1\text{-}14}$), where G_1 represents the sub-segmental bronchi, G_2 represents the sub-sub-segmental bronchi, etc. For statistical analysis, we used the median BA measurements of $G_{1\text{-}6}$ because these bronchial generations included the highest number of BA measurements in most participants and which is less affected by body size, inspiration level, and the relatively higher visibility of small airways affected by airway disease.[7, 9] On the request of the reviewer, we conducted an additional analysis focusing on BA measurements in $G_{1\text{-}3}$ to address a concern regarding the reliability of measurements in higher generations. This analysis confirmed that the main findings of the primary analysis were consistent with proximal-generation airways ($G_{1\text{-}3}$). See online supplement.

LungQ-MP also uses AI-based algorithms to detect mucus plugs throughout the lung and has now been used in multiple real-life cohorts of patients with COPD, cystic fibrosis and bronchiectasis.[11-13] The detection algorithm, trained on expert annotations, identifies full mucus obstructions with clear proximal and distal airways, providing both location and volumetric assessments. The segmentation combines seed-based and voxel-based methods, providing detection and quantification of mucus plugs

along the entire bronchi, including the peripheries. The algorithm provides output as the number of detected mucus plugs and their segmental locations and volumes (mm^3).

Variables of interest

- Bronchial wall thickness: B_{wt}/A, B_{wa}/B_{oa}, and Pi10
- Bronchial inner diameter: B_{in}/A
- Mucus plugs: total number of detected mucus plugs in the bronchial tree and total mucus plug volume (mm^3)
- Spirometry: FEV_1 %predicted, FEV_1/FVC ratio
- Blood eosinophil counts in number of cells*10^9/L and historical measurements ≥0.3*10^9/L
- Patient factors: age, BMI, mMRC dyspnoea scores, bacterial colonisation (*Pseudomonas aeruginosa* and other pathogens), number of exacerbations and hospitalisations, FACED and BSI scores.

Primary research questions

- Relationship between
  - BA measurements of bronchial wall thickness (B_{wt}/A, B_{wa}/B_{oa}, B_{in}/A) with spirometry (FEV_1 % predicted and FEV_1/FVC)
  - Mucus plug measurements (total number and volume) with spirometry
- Relationship between
  - BA measurements of bronchial wall thickness (B_{wt}/A, B_{wa}/B_{oa}) with blood eosinophils (number of cells*10^9/L and binary for historical value >0.3*10^9/L)
  - Measurements of mucus plugs (total number and volume) with blood eosinophils

Secondary research questions

- Relationship between automated measurements of Pi10 and B_{in}/A with spirometry and eosinophil counts
- Relationship between mucus plug number and volume with bronchiectasis severity models (BSI and FACED)
- Relationship between clinical characteristics (age, dyspnoea, exacerbation frequency, eosinophil counts, *Pseudomonas* colonisation and FEV_1 %predicted) with BA-measurements of bronchial wall thickness and mucus plugs.

Statistical analysis

Data are presented as median and interquartile range (IQR) (25^{th} -75^{th} percentile) or as mean ± standard deviation (SD), depending on the data distribution.

B_{wt}/A, B_{wa}/B_{oa}, Pi10, and B_{in}/A were selected as the most relevant measures for the connection with spirometry outcomes, as the bronchial internal diameter of the airways and the bronchial wall area are likely to determine maximal flows for a spirometry manoeuvre. For the spirometry outcomes FEV_1% predicted and FEV_1/FVC were selected because these outcomes are considered dependent on airway resistance and airway dimensions. The relationship between the total number of mucus plugs, total mucus volume, and spirometry was investigated. Correlations were assessed using Spearman's, Pearson's, or point bi-serial coefficients and confidence intervals, depending on data skewness. A correlation coefficient lower than 0.2 was rated as very weak, 0.2-0.4 as weak, 0.4-0.6 as moderate, 0.6-0.8 as strong, and 0.8-1 as excellent.[30]

Multiple regression analyses were performed using clinical characteristics age, mMRC dyspnoea score, number of exacerbations in the preceding year, blood eosinophil counts in cells*10^9/L, *Pseudomonas aeruginosa* colonisation, and FEV_1 percentage predicted as independent variables, and measures of bronchial wall thickening (B_{wt}/A and B_{wa}/B_{oa}) and mucus plugs (total number and volume) as dependent variables.

Age, blood eosinophil count, and FEV_1 were taken as continuous variables, *Pseudomonas aeruginosa* as binary variable and mMRC dyspnoea score and exacerbations per year as categorical variables using 0, 1 and ≥2, with reference 0. The PP-plots were checked for normality of the residuals. Initial analyses included all participants; however, residuals suggested deviation from normality. Outlier analysis was conducted based on standard deviation (≥3SD) and Cook's distance (≥0.5). Statistical analysis was performed using SPSS version 28.0.1.0 (IBM, USA), with significance defined as $p < 0.05$, without corrections for multiple testing.

Results

LungQ successfully measured BA and mucus plugs in 63 and 59 participants, respectively. Of the 63 participants, 35 were women (55.6%), mean age 60.8 (±17.2) years. Most participants were Caucasian (76.2%), and 34.9% had a history of smoking (no current smokers). All participants were prescribed inhaled corticosteroids (ICS); no participants were prescribed maintenance oral corticosteroids. In 63 participants, LungQ measured 12528 BA pairs, of which generations 1-6 account for 93.7% (11,709/12,528).

For complete participant characteristics, see Table 1. For a depiction of median B_{in}/A, B_{wt}/A, and B_{wa}/B_{oa} ratios for bronchial generations 1-6 see supplemental Figure 1a-c, as well as a bar chart of participants sorted by number of mucus plugs in supplemental

Table 1. Participant characteristics

Clinical characteristics	
Gender (female)	55.6% (n=35)
Age (years)	60.8 (±17.2)
BMI (kg/m^2)	23.77 (±4.56)
Ethnicity (Caucasian, binary)	76.2% (n=48)
Former smoking (binary)	34.9% (n=22)
Bronchiectasis aetiology	
ABPA	1 (1.6%)
Asthma	10 (15.9%)
Connective Tissue Disease	2 (3.2%)
GERD/aspiration	1 (1.6%)
Idiopathic	10 (15.9%)
Immunodeficiency	8 (12.7%)
Non-Tuberculous Mycobacteria	2 (3.2%)
PCD	2 (3.2%)
Post-infectious	8 (12.7%)
More than one aetiological factor / other	19 (30.2%)
BSI-score	6.0 (3.0-8.0)
0- 4 points: Mild Bronchiectasis	24 (38.1%)
5–8 points: Moderate Bronchiectasis	24 (38.1%)
≥9 points: Severe Bronchiectasis	15 (23.8%)
FACED-score	2.0 (1.0-3.0)
0-2 points: Mild bronchiectasis	42 (66.7%)
3-4 points: Moderate bronchiectasis	18 (28.6%)
5-7 points: Severe bronchiectasis	3 (4.8%)
Number of exacerbations/year	1.0 (0.0-1.0)
0 Exacerbations	25 (39.7%)
1 Exacerbation	23 (36.5%)
≥2 ('Frequent exacerbator')	15 (23.8%)
mMRC dyspnoea score	0.0 (0.0-1.0)
0: Only with strenuous exercise)	32 (50.8%)
1: When hurrying or walking up a slight hill	16 (25.4%)
≥2: Walks slower than same age, must stop for breath, or worse	15 (23.8%)
Blood eosinophil count, 10^9/L (continuous)	0.26 (±0.32)
Eosinophils ever ≥0.3 *10^9/L (binary)	46.0% (n=29)
Pseudomonas colonisation (binary)	30.2% (n=19)
Other pathogen colonisation (binary)	42.9% (n=27)
Use of azithromycin (binary)	55.6% (n=35)
FEV_1 %predicted	71.30 (±21.75)
FER (FEV_1/FVC)	0.64 (±0.13)

Table 1. Continued

Clinical characteristics	
Radiological characteristics	
B_{wt}/A (G_{1-6})	0.16 (±0.1)
B_{wa}/B_{oa} (G_{1-6})	0.43 (±0.15)
B_{in}/A (G_{1-6})	0.96 (±0.39)
Pi10 (mm^2)	2.47 (±0.47)
Total number of mucus plugs	9.0 (2.0-20.5)
Total mucus volume (mm^3)	0.44 (0.11-1.67)
Total number of BA pairs (all generations), mean per participant	12528, 199
Generation 1 (G_1)	1380, 22
Generation 2 (G_2)	2643, 42
Generation 3 (G_3)	3054, 48
Generation 4 (G_4)	2328, 37
Generation 5 (G_5)	1493, 24
Generation 6 (G_6)	811, 15

Figure 2. See Supplemental Table 1 for the CT scanner manufacturers, kernels and slice thickness of the included scans.

1. Relationship between bronchial wall thickness, mucus plugs and lung function.

Correlations between bronchial parameters and lung function tests were observed (Table 2). B_{wt}/A and B_{wa}/B_{oa} demonstrated weak and moderate negative correlations with FEV_1 % predicted and FEV_1/FVC, indicating that increases in these bronchial wall parameters are associated with lower lung function. Similarly, Pi10 showed moderate negative correlations with both FEV_1% predicted and FEV_1/FVC. In contrast, B_{in}/A showed moderate positive correlation. The total number of mucus plugs and total mucus plug volume also showed moderate to strong negative correlations with both FEV_1 % predicted and FEV_1/FVC. Correlation plots for all investigated relationships are shown in supplemental Figure 3a-c.

Table 2. Correlations between radiological measures and lung function

Parameter	FEV_1 % predicted	FEV_1 % predicted	FEV_1/FVC	FEV_1/FVC
	Rho	CI	Rho	CI
$B_{wt}/A\ G_{1-6}$	-0.366	(-0.59, -0.09)	-0.297	(-0.54, -0.02)
$B_{wa}/B_{oa}\ G_{1-6}$	-0.467	(-0.67, -0.23)	-0.452	(-0.66, -0.22)
Pi10	-0.501	(-0.70, -0.25)	-0.502	(-0.70, -0.27)
B_{in}/A_{G1-6}	0.331	(0.10, 0.53)	0.379	(0.15, 0.58)
Total number of mucus plugs	-0.394	(-0.63, -0.11)	-0.602	(-0.73, -0.40)
Total mucus plug volume	-0.333	(-0.56, -0.07)	-0.547	(-0.70, -0.33)

Correlations were calculated using Spearman's rho. CI: confidence interval.

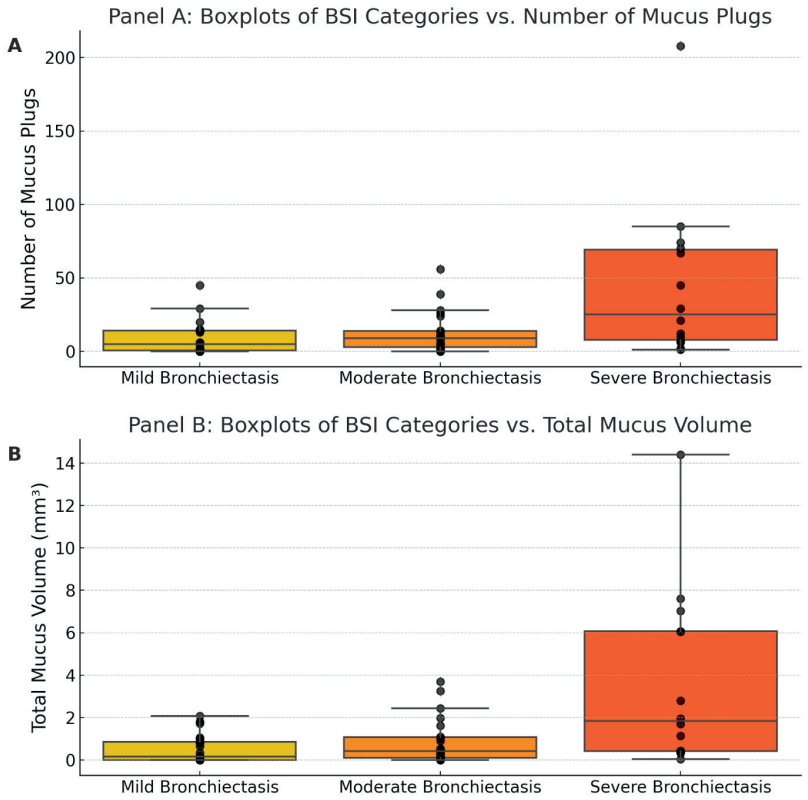


Figure 3a and 3b. Boxplots of mucus plugs and volume by BSI score category.

Boxplots indicating the median number of plugs and median total mucus volume, interquartile range (box), smallest and largest values within 1.5 IQR (whiskers), and outliers.

2. Relationship between bronchial wall thickness and mucus plugs with blood eosinophil counts:

Correlation coefficients revealed very weak associations between bronchial dimensions parameters of B_{wt}/A, B_{wa}/B_{oa}, Pi10, and B_{in}/A with both continuous and binary eosinophil measures. The total number of mucus plugs and total mucus plug volume were very weakly correlated with eosinophil measures. (Table 3)

Table 3. Correlations between radiological measures and eosinophil counts

Parameter	Continuous Eosinophils		Eosinophils Ever ≥0.3*10^9	
	Rho (Spearman)	CI	r (point bi-serial)	CI
B_{wt}/A_{G1-6}	-0.039	(-0.33, 0.23)	0.079	(-0.23, 0.29)
B_{wa}/B_{oa} G_{1-6}	0.072	(-0.22, 0.34)	0.142	(-0.07, 0.41)
Pi10	0.085	(-0.22, 0.36)	0.127	(-0.13, 0.39)
B_{in}/A_{G1-6}	-0.068	(-0.34, 0.21)	-0.177	(-0.39, 0.12)
Total number of mucus plugs	0.094	(-0.15, 0.35)	-0.065	(-0.29, 0.22)
Total mucus plug volume	0.093	(-0.19, 0.37)	-0.071	(-0.36, 0.16)

Correlations were calculated using Spearman's rho and point bi-serial. CI: confidence interval.

3. Relationship between patient factors and bronchial wall thickness and mucus plug parameters.

Moderate positive correlations were observed between both BSI and FACED scores and the total mucus volume and number of mucus plugs. (Table 4 and Figure 3a-b, also supplemental Figure 4a-b)

Table 4. Correlations between radiological measures and bronchiectasis severity scores

Parameter	BSI		FACED	
	Rho	CI	Rho	CI
B_{wt}/A G_{1-6}	0.334	(0.10, 0.54)	0.329	(0.09, 0.52)
B_{wa}/B_{oa} G_{1-6}	0.151	(-0.09, 0.39)	0.205	(-0.02, 0.42)
Pi10	0.175	(-0.10, 0.42)	0.217	(-0.03, 0.45)
B_{in}/A_{G1-6}	0.022	(-0.23, 0.26)	-0.022	(-0.28, 0.21)
Total number of mucus plugs	0.446	(0.219, 0.672)	0.441	(0.217, 0.632)
Total mucus plug volume	0.494	(0.274, 0.714)	0.473	(0.253, 0.647)

Correlations were calculated using Spearman's rho. CI: confidence interval.

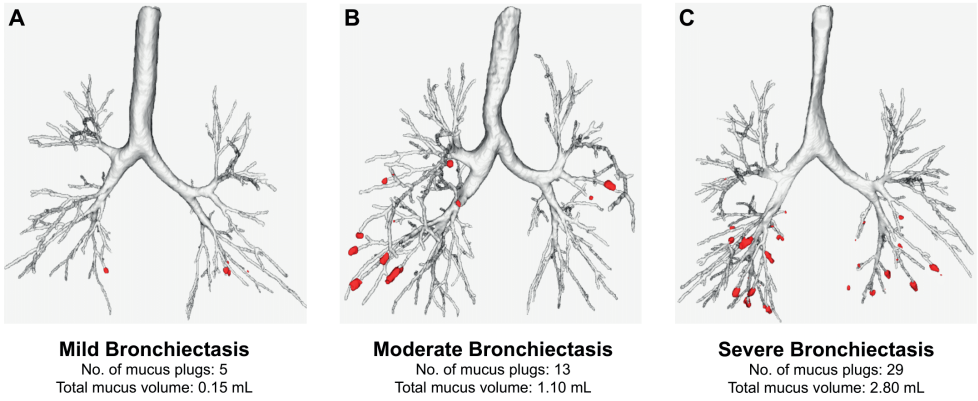


Figure 4. 3D Renderings of Mucus Plugs in Participants with Varying Degrees of Bronchiectasis Severity

This figure displays representative examples of mucus plugs in participants with mild (A), moderate (B), and severe (C) bronchiectasis, as categorized by the Bronchiectasis Severity Index (BSI). The 3D renderings show the bronchial tree, with mucus plugs highlighted in red. These examples represent participants with mucus plug counts near the median for their respective BSI category.

In multiple regression models including the clinical characteristics of age, mMRC dyspnoea score, blood eosinophil counts, no. of exacerbations/year, *Pseudomonas aeruginosa* colonisation, and FEV_1 %predicted, a consistent negative association was found between measures of bronchial wall thickness (B_{wt}/A, B_{wa}/B_{oa}) and FEV_1% predicted, a positive association with *Pseudomonas* colonisation, and a positive association with ≥2 exacerbations per year ('frequent exacerbators'). The same associations were observed for both the total number of mucus plugs and total mucus volume.

Analysis with the full cohort revealed non-normal residuals in PP-plots for the mucus models, to the influence of one outlier on the number and volume of mucus plugs at +5SD and Cook's distance 0.53. Upon removal of this outlier, the residuals' normality improved, and the strength of the associations for FEV_1, *Pseudomonas* and exacerbations increased. In addition, an association for mMRC ≥2 was seen. The comparative results of all models are shown in Table 5 and Supplemental Table 2. The comparative analysis of BA measures in bronchial generations 1-3 are shown in Supplemental Tables 3a-e.

Table 5.

Multiple regression results for the full cohort showing associations between independent participant characteristics as predictor variables for depent variables of BA-measures of bronchial wall thickness and mucus plug number and volume.

Variable	Model: B_{wt}/A G_{1-6} Coeff.	Model Sig.	Model: B_{wa}/B_{oa} G_{1-6} Coeff.	Model Sig.	Model: No. of Plugs Coeff.	Model Sig.	Model: Mucus Volume Coeff.	Model Sig.
Constant	.384	< .001	.564	< .001	38.315	.054	2.147	.143
Age	.000	.799	-.001	.279	.178	.433	.014	.403
Eosinophils	-.012	.664	.023	.499	-2.412	.835	-.155	.857
FEV_1%	-.002	**< .001**	-.002	**.001**	-.526	**.006**	-.034	**.017**
Pseudomonas	.056	**.006**	.066	**.008**	22.519	**.007**	1.794	**.004**
Exac 1 vs. 0	-.004	.850	<-0.0001	.998	.559	.947	.025	.968
Exac ≥2 vs. 0	.056	**.022**	.045	.129	21.417	**.026**	1.796	**.012**
mMRC 1 vs. 0	-.004	.856	-.011	.699	-8.016	.375	-.431	.519
mMRC ≥2 vs. 0	-.034	.184	-.019	.542	-8.155	.426	-1.146	.847

Discussion

This study aimed to investigate the relationships between automatic image analysis metrics for bronchial wall thickness, mucus plugs, and clinical parameters in a cohort of bronchiectasis disease patients with an asthma co-diagnosis. The findings indicate that thicker bronchial walls and greater mucus plug numbers and volumes are associated with reduced FEV_1 percentage predicted and FEV_1/FVC ratios. This negative association underscores the impact of structural changes of the bronchial wall and mucus obstruction, as assessed by automated CT analysis, on spirometry metrics *in vivo*, supporting previous findings on the significance of bronchial wall thickening in asthma, bronchiectasis, and COPD.[31-33]

The airway lumen dimension, measured as B_{in}/A, showed a weakpositive correlation with lung function, whereas bronchial wall thickness measured as B_{wa}/B_{oa} and Pi10 had moderate associations. The airway lumen size varies with thoracic volume during imaging, making it less consistent as a functional indicator. In contrast, increased airway wall thickness is linked to greater stiffness, reduced compliance and reactivity. [34] These findings suggest that these bronchial wall measurements are more reliable markers for linking structure to lung function.

Absent correlations between blood eosinophil counts and bronchial wall thickness or mucus plugs suggest a limited role for eosinophil-driven inflammation in this cohort. Previous research links increased bronchial wall area to higher sputum eosinophil counts and reduced lung function in eosinophilic asthma patients. [29] Mucus plugging is also a common phenomenon in asthma, associated with eosinophils and other type 2 inflammatory features, as well as changes in airflow obstruction. [15, 35] However, in this cohort, the prescription of ICS in all participants may have attenuated any eosinophilic inflammation. Secondly, the recruitment of participants from a specialised bronchiectasis clinic suggests a predominance of neutrophilic inflammation or mixed inflammatory pathways. Third, the instability of single blood eosinophil measurements in bronchiectasis may influence these results.[36] Categorizing patients based on historical blood eosinophil levels ≥0.3*109/L to indicate an eosinophilic endotype did not reveal an important relationship either.[16] Future studies may use other ways of assessing the presence of eosinophilic inflammation such as longitudinal blood measurements, eosinophil/neutrophil ratios or sputum lateral flow assays.[37]

Positive correlations between BSI and FACED scores with mucus plug numbers and volumes support the role of mucus metrics as biomarkers of underlying inflammation and disease severity. According to the vicious vortex hypothesis, mucus production and impaired mucociliary clearance act both as a result of and as a contributor to disease progression.[2] Mucus plugs have been associated with all-cause mortality in COPD, underscoring their high clinical relevance.[38] Future studies may also position CT mucus analyses for risk assessment in bronchiectasis disease, potentially offering an efficient alternative to composite risk scores.

BA and Pi10 analyses showed similar correlations with lung function, indicating their comparable value as markers for bronchial wall thickening. B_{wa}/B_{oa} and B_{wt}/A ratios may directly reflect airway remodeling across various airway sizes and can also be used for sectional bronchial tree analysis, while Pi10 provides a standardized measure for broader comparisons across patient populations. However, B_{wt}/A may be influenced by arterial size variations, potentially not reflecting airway changes alone.

In multiple regression analysis, bronchial wall thickness was negatively associated with FEV_1 % predicted and positively with *Pseudomonas* colonisation, supporting the pathogen's detrimental role in exacerbations and disease progression.[39, 40] These results align with the models for mucus plug numbers and volumes, showing similar associations with *Pseudomonas* and FEV_1, and an independent relationship with frequent exacerbations. The linkage between radiological extent of airway changes, *Pseudomonas* colonisation, and severe exacerbations was recently also demonstrated in a large radiological analysis of 524 EMBARC patients.[4]

Quantitative CT imaging provides detailed, reproducible data on airway dimensions and mucus plugs, enhancing our understanding of disease mechanisms. These metrics link structural changes to clinical outcomes like exacerbation frequency and lower lung function.[8, 33] Clinically, quantitative CT analysis may aid in risk stratification and differentiate inflammatory phenotypes to identify patients who may benefit from various treatment options. Moreover, the incorporation of automated quantitative CT analysis meets the widely recognized need for noninvasive and time-efficient biomarkers in bronchiectasis.[5] In this analysis, multiple metrics of bronchial wall thickness and mucuc plugs were investigated and each showed important associations with clinical characteristics. The relative value of each metric will be further evaluated in future studies. Also, the total number of mucus plugs has been investigated in previous studies, while the total mucus volume remains largely unexplored. Mucus volume may be particularly valuable in longitudinal studies where mucus plug presence and/or persistence can be weighed against an increase or decrease in volume. Although the algorithm performs highly accurately, occasional underestimation of mucus plugs may occur, similar to visual assessments. This potential underestimation is primarily due to limitations in detecting smaller or peripheral plugs.

A key limitation of our study is its retrospective design and relatively small sample size, limiting statistical power and the number of independent patient characteristics in our regression models. Additionally, the cross-sectional nature of the study prevents investigation of temporal relationships. Prospective longitudinal studies with larger cohorts and control groups of bronchiectasis without asthma, as well as asthma without bronchiectasis, are needed to validate our findings on the impact of bronchial wall thickness and mucus plugs and to further explore the role of eosinophils in bronchiectasis-asthma overlap.

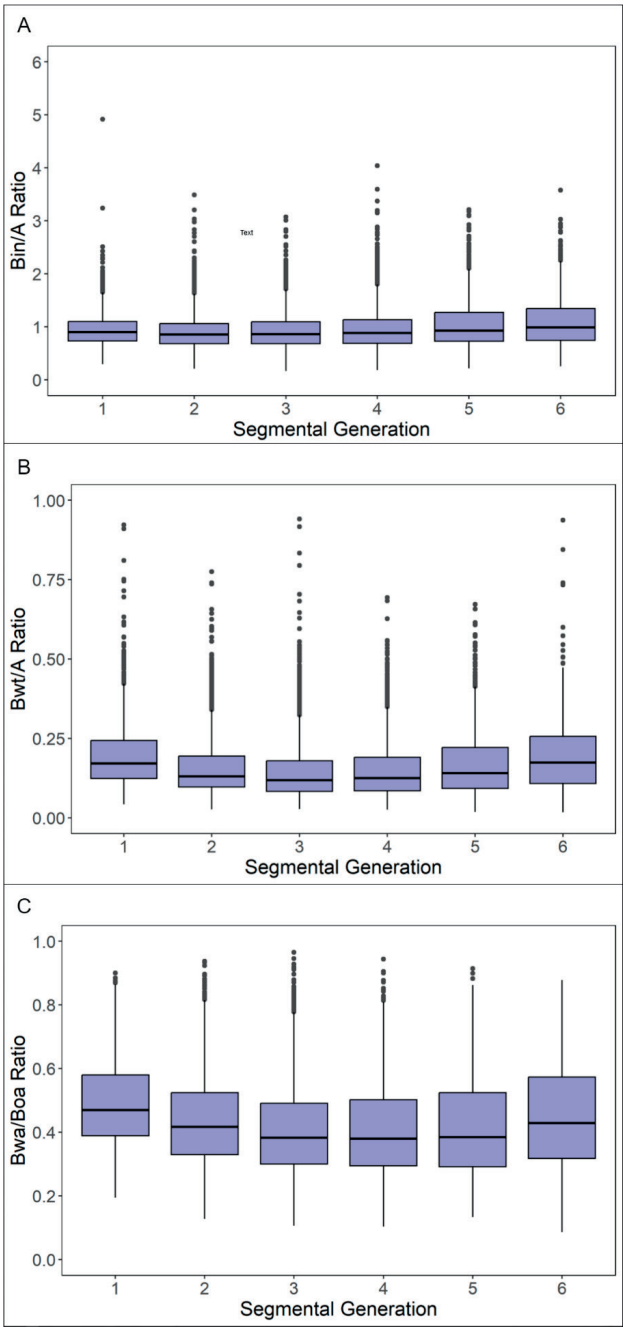
Conclusion

This study observed important relationships between on the one hand automated measurements of bronchial wall thickness and mucus plugs and on the other hand spirometry metrics and bronchiectasis severity scores, as well as independent associations for FEV_1, *Pseudomonas aeruginosa*, and frequent exacerbations. No clear relationship with blood eosinophil counts was observed in this cohort of patients with bronchiectasis disease and asthma co-diagnosis. These findings illustrate the high potential of quantitative imaging biomarkers to enhance clinical studies, improve risk assessment, enable phenotyping, and facilitate the development of tailored treatment strategies for bronchiectasis disease patients.

References

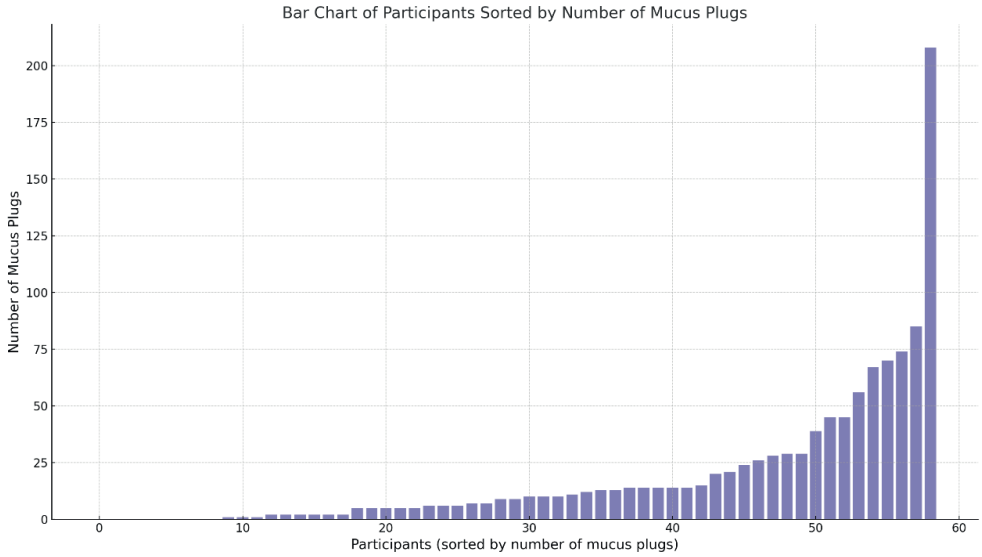
1. Aliberti, S., et al., *Criteria and definitions for the radiological and clinical diagnosis of bronchiectasis in adults for use in clinical trials: international consensus recommendations.* Lancet Respir Med, 2022. **10**(3): p. 298-306.
2. Flume, P.A., J.D. Chalmers, and K.N. Olivier, *Advances in bronchiectasis: endotyping, genetics, microbiome, and disease heterogeneity.* Lancet, 2018. **392**(10150): p. 880-890.
3. Long, M.B., et al., *Rethinking bronchiectasis as an inflammatory disease.* Lancet Respir Med, 2024.
4. Pieters, A.L.P.p., et al., *Structural Lung Disease and Clinical Phenotype in Bronchiectasis Patients: The EMBARC CT Study.* Am J Respir Crit Care Med, 2024.
5. Johnson, E., M.B. Long, and J.D. Chalmers, *Biomarkers in bronchiectasis.* Eur Respir Rev, 2024. **33**(173).
6. Chen, Y., et al., *Automatic bronchus and artery analysis on chest computed tomography to evaluate the effect of inhaled hypertonic saline in children aged 3-6 years with cystic fibrosis in a randomized clinical trial.* J Cyst Fibros, 2023.
7. Lv, Q., et al., *Automatic analysis of bronchus-artery dimensions to diagnose and monitor airways disease in cystic fibrosis.* Thorax, 2023.
8. Díaz, A.A., et al., *Artificial Intelligence-based CT Assessment of Bronchiectasis: The COPDGene Study.* Radiology, 2023. **307**(1): p. e221109.
9. Pieters, A.L.P., et al., *Automated method of bronchus and artery dimensions of an adult bronchiectasis population.* ERJ Open Research, 2024: p. 00231-2024.
10. van den Bosch, W.B., et al., *Children with severe asthma have substantial structural airway changes on computed tomography.* ERJ Open Res, 2024. **10**(1).
11. Tiddens, H.A.W.M., et al., *Automatic analysis of bronchus-artery ratios and mucus plugs of 640 chest CTs of EMBARC bronchiectasis patients*, in *European Respiratory Society Congress 2024*. 2024, European Respiratory Society: Vienna.
12. McNally, P., et al., *WS15.05 Improvements in structural lung disease in people with CF aged 12 and above on elexacaftor/tezacaftor/ivacaftor are sustained for up to two years*, in *Abstracts of the 47th European Cystic Fibrosis Conference*. 2024, Journal of Cystic Fibrosis.
13. Tiddens, H.A.W.M., et al., *Fully Automated Mucus Plug Quantification on Chest CTs and Its Correlation With All-cause Mortality*, in *American Thoracic Society (ATS) International Conference Abstracts: A101. FULL METAL JACKET TARGETING COPD AND CHRONIC AIRWAYS DISEASE*. 2024. p. A2778-A2778.
14. Guan, W.J., et al., *Significance and Potential Role of Eosinophils in Non-Cystic Fibrosis Bronchiectasis.* J Allergy Clin Immunol Pract, 2023. **11**(4): p. 1089-1099.
15. Dunican, E.M., et al., *Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction.* J Clin Invest, 2018. **128**(3): p. 997-1009.
16. Shoemark, A., et al., *Characterization of Eosinophilic Bronchiectasis: A European Multicohort Study.* Am J Respir Crit Care Med, 2022. **205**(8): p. 894-902.
17. Heaney, L.G., et al., *Eosinophilic and Noneosinophilic Asthma: An Expert Consensus Framework to Characterize Phenotypes in a Global Real-Life Severe Asthma Cohort.* Chest, 2021. **160**(3): p. 814-830.
18. Polverino, E., et al., *The overlap between bronchiectasis and chronic airway diseases: state of the art and future directions.* Eur Respir J, 2018. **52**(3).
19. Tiotiu, A., et al., *Does asthma-bronchiectasis overlap syndrome (ABOS) really exist?* J Asthma, 2023: p. 1-7.

20. Polverino, E., et al., *Bronchiectasis and asthma: Data from the European Bronchiectasis Registry (EMBARC).* J Allergy Clin Immunol, 2024.
21. Chung, W.S. and C.L. Lin, *Acute respiratory events in patients with bronchiectasis-COPD overlap syndrome: A population-based cohort study.* Respir Med, 2018. **140**: p. 6-10.
22. Chalmers, J.D., et al., *Bronchiectasis in Europe: data on disease characteristics from the European Bronchiectasis registry (EMBARC).* Lancet Respir Med, 2023. **11**(7): p. 637-649.
23. Bendien, S.A., et al., *Bronchiectasis in Severe Asthma: Does It Make a Difference?* Respiration, 2020: p. 1-9.
24. Donovan, G.M. and P.B. Noble, *Small airways vs large airways in asthma: time for a new perspective.* J Appl Physiol (1985), 2021. **131**(6): p. 1839-1841.
25. Graham, B.L., et al., *Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement.* Am J Respir Crit Care Med, 2019. **200**(8): p. e70-e88.
26. Werf, T.v.d.e.a. *NVALT richtlijn Bronchiëctasieën*. 2017 06-19-2017 [cited 2024 05-27-2024]; Available from: https://richtlijnendatabase.nl/richtlijn/bronchiectasieen/startpagina_bronchiectasieen.html.
27. Martinez-Garcia, M.A., et al., *Multidimensional approach to non-cystic fibrosis bronchiectasis: the FACED score.* Eur Respir J, 2014. **43**(5): p. 1357-67.
28. Minov, J., et al., *Assessment of the Non-Cystic Fibrosis Bronchiectasis Severity: The FACED Score vs the Bronchiectasis Severity Index.* Open Respir Med J, 2015. **9**: p. 46-51.
29. Grydeland, T.B., et al., *Quantitative computed tomography: emphysema and airway wall thickness by sex, age and smoking.* Eur Respir J, 2009. **34**(4): p. 858-65.
30. Koo, T.K. and M.Y. Li, *A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research.* J Chiropr Med, 2016. **15**(2): p. 155-63.
31. Kim, J.H., et al., *Relationships Between High-Resolution Computed Tomographic Features and Lung Function Trajectory in Patients With Asthma.* Allergy Asthma Immunol Res, 2023. **15**(2): p. 174-185.
32. Yamamoto, Y., et al., *Impact of bronchial wall thickness on airflow obstruction in bronchiectasis.* Respir Physiol Neurobiol, 2022. **295**: p. 103788.
33. Mohamed Hoesein, F.A., et al., *Airway wall thickness associated with forced expiratory volume in 1 second decline and development of airflow limitation.* Eur Respir J, 2015. **45**(3): p. 644-51.
34. Akio, N., et al., *Relationship of Airway Wall Thickness to Airway Sensitivity and Airway Reactivity in Asthma.* American Journal of Respiratory and Critical Care Medicine, 2003. **168**(8): p. 983-988.
35. Al-Shaikhly, T., et al., *Location of eosinophils in the airway wall is critical for specific features of airway hyperresponsiveness and T2 inflammation in asthma.* Eur Respir J, 2022. **60**(2).
36. Martinez-Garcia, M.A., et al., *Reliability of blood eosinophil count in steady-state bronchiectasis.* Pulmonology, 2024.
37. Ali, M.M., et al., *A Rapid Sputum-based Lateral Flow Assay for Airway Eosinophilia using an RNA-cleaving DNAzyme Selected for Eosinophil Peroxidase.* Angewandte Chemie-International Edition, 2023. **62**(38).
38. Diaz, A.A., et al., *Airway-Occluding Mucus Plugs and Mortality in Patients With Chronic Obstructive Pulmonary Disease.* JAMA, 2023. **329**(21): p. 1832-1839.
39. Araújo, D., et al., *The independent contribution of Pseudomonas aeruginosa infection to long-term clinical outcomes in bronchiectasis.* Eur Respir J, 2018. **51**(2).
40. Vidaillac, C. and S.H. Chotirmall, *Pseudomonas aeruginosa in bronchiectasis: infection, inflammation, and therapies.* Expert Rev Respir Med, 2021. **15**(5): p. 649-662.

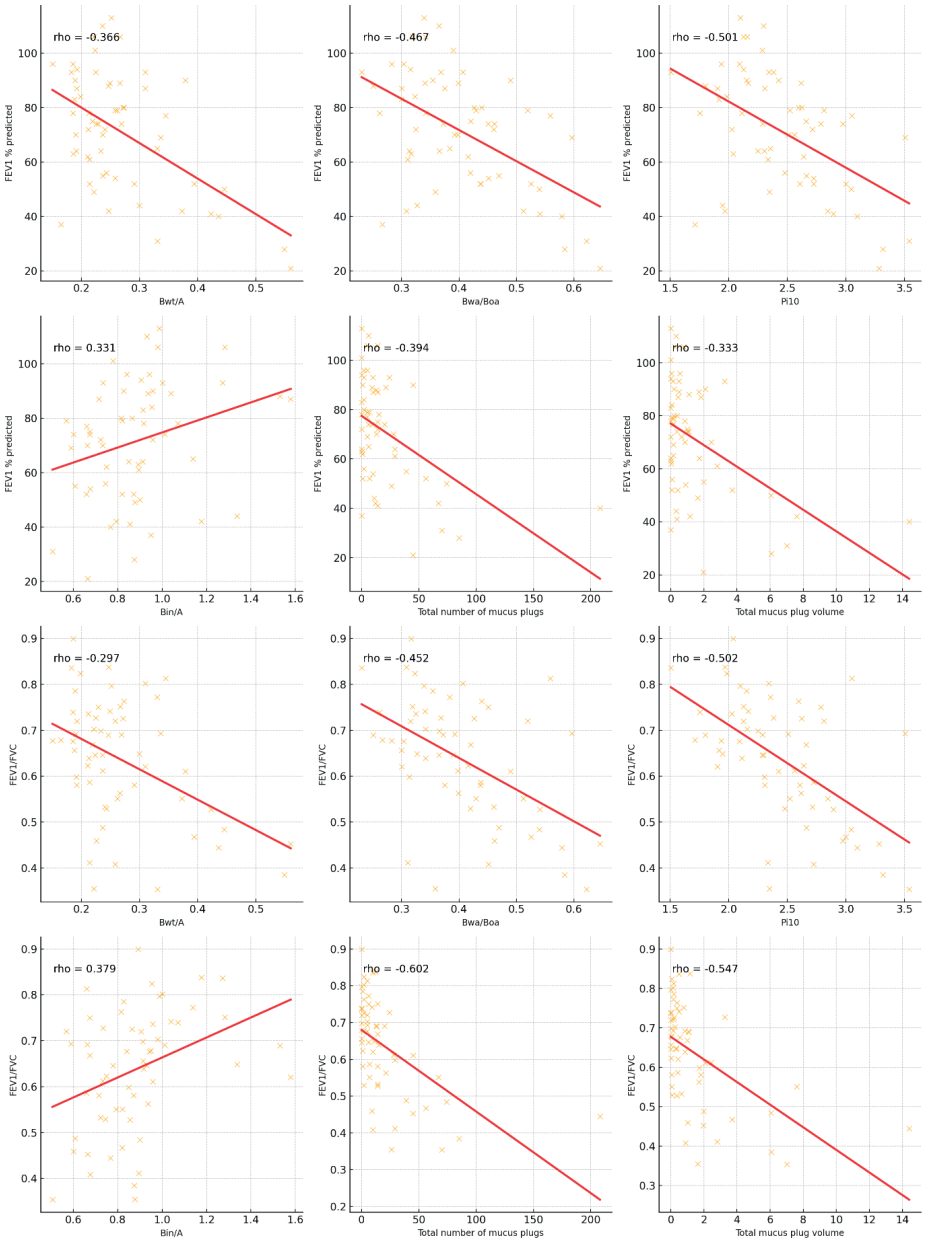


Supplemental Figures 1a, 1b and 1c.

Boxplots of B_{in}/A, B_{wt}/A, and B_{wa}/B_{oa} ratios for bronchial segmental generations 1-6, depicting medians, IQR, range +/-1.5 IQR and outliers. A) B_{in}/A ratios; B) B_{wt}/A ratios; C: B_{wa}/B_{oa} ratios.

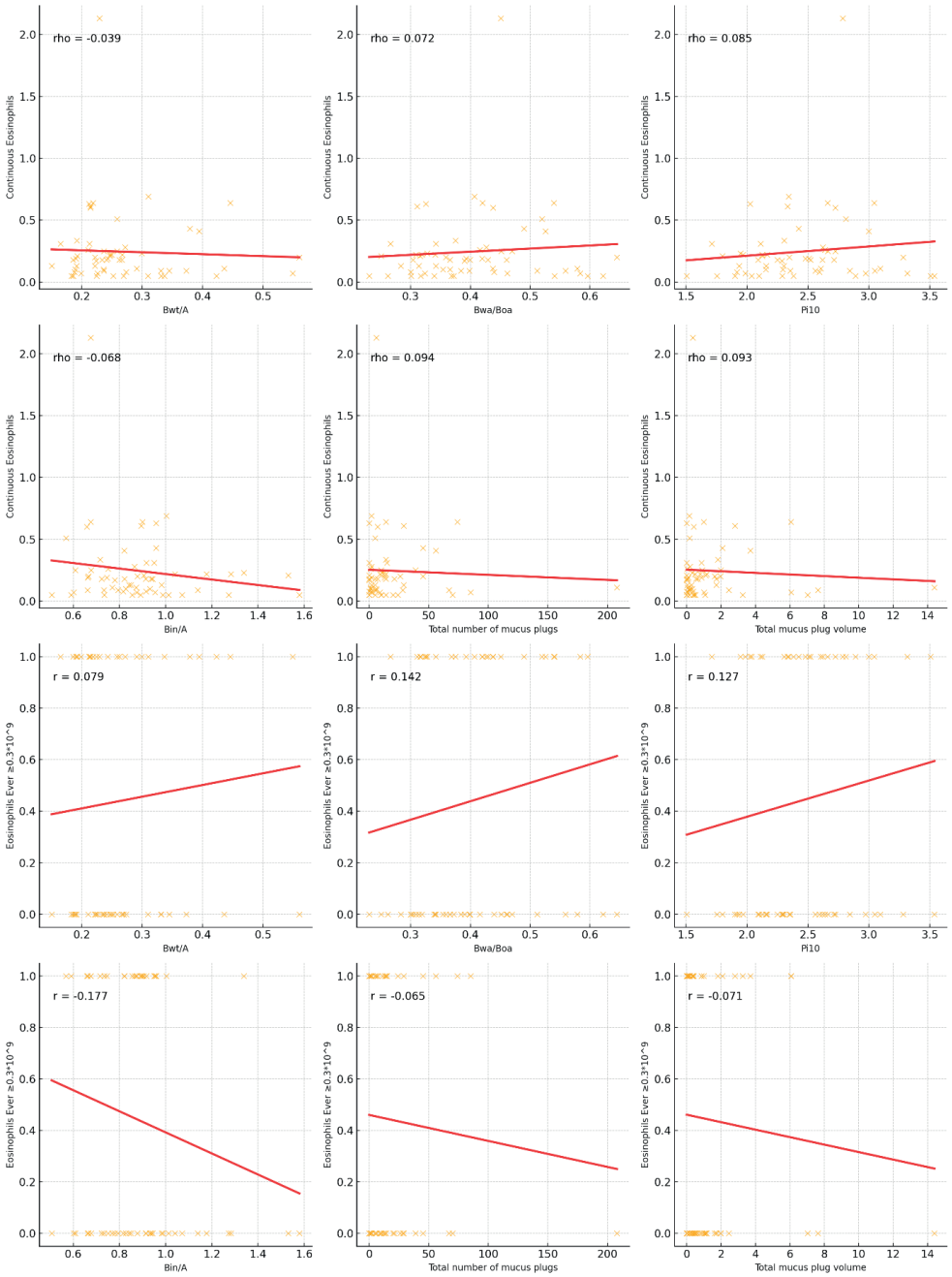


Supplemental Figure 2. Bar chart of participants sorted by the total number of mucus plugs.

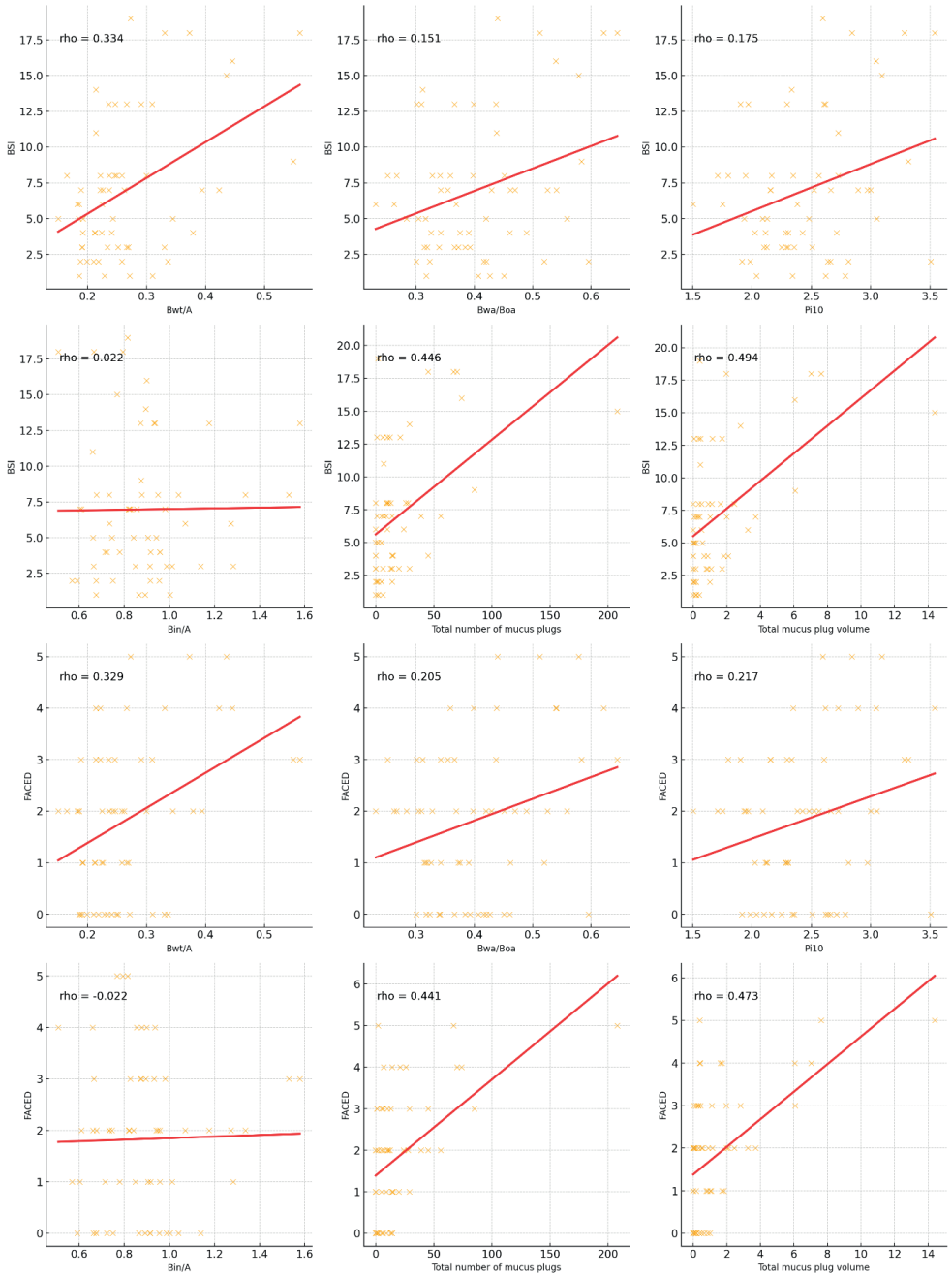


Supplemental Figure 3a-c. Correlation plots for relationships investigated in manuscript table 2, table 3 and table 4.

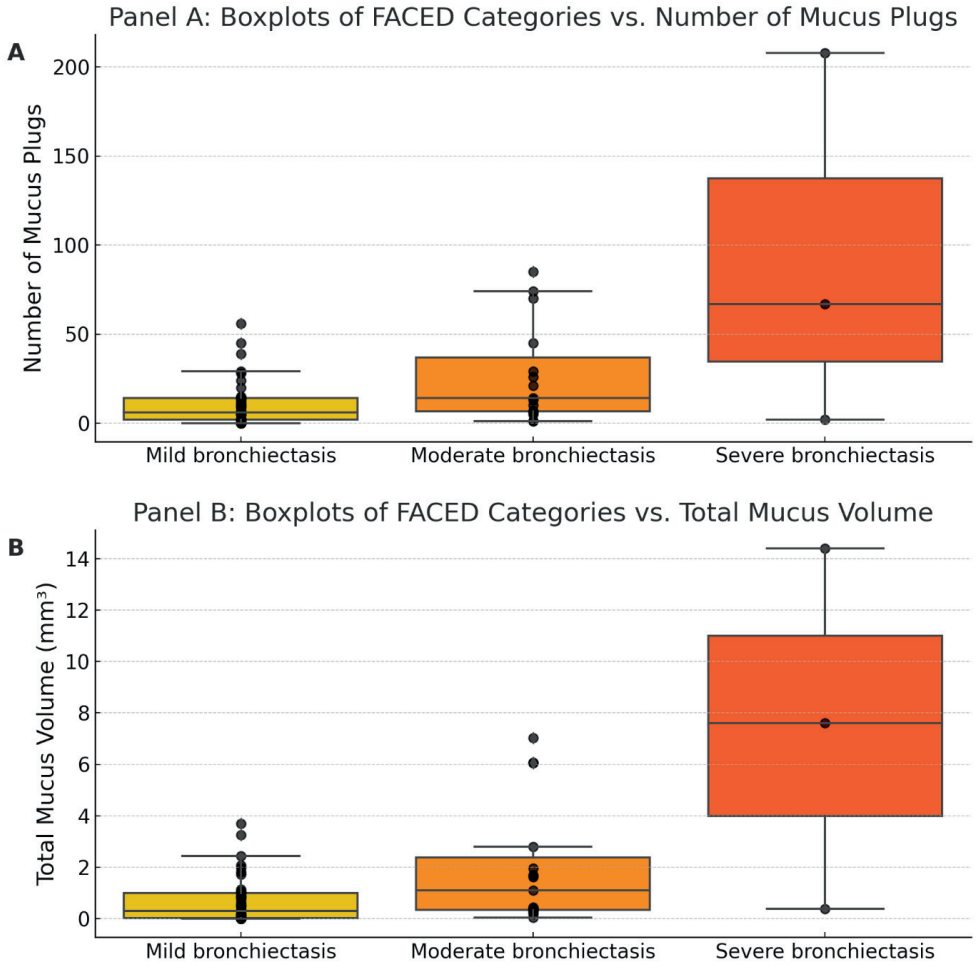
3a. Spearman's correlations between radiological parameters (B_{wt}/A, B_{wa}/B_{oa}, Pi10, B_{in}/A, mucus plugs, and mucus plug volume) and lung function measures (FEV1 % predicted, FEV1/FVC). Scatter plots display data points, regression lines, and the rho values.



3b. Correlation plots illustrating the relationships between radiological parameters and eosinophil counts, including continuous eosinophils (Spearman's rho) and eosinophils ever ≥0.3*10^9 (point-biserial r). Data points, regression lines, and correlation values are presented.



3c. Correlation plots showing correlations between radiological parameters and bronchiectasis severity scores (BSI and FACED). Scatter plots include rho values, regression lines, and data points.



Supplemental Figures 4a and 3b. Boxplots of mucus plugs and volume by FACED score category.

Boxplots indicating the median number of plugs and median total mucus volume, interquartile range (box), smallest and largest values within 1.5 IQR (whiskers), and outliers.

Supplemental Table 1.

This table details the CT scanner manufacturers, reconstruction kernels, slice thicknesses, and the number of scans included in the study.

CT Scanner Manufacturer	Reconstruction Kernel	Slice Thickness (mm)	Count
PHILIPS	IMR1,SharpPlus	1.5	1
SIEMENS	B70f	1.0	3
SIEMENS	B75f	1.0	1
SIEMENS	Bl57d\3	1.0	9
SIEMENS	Bl57f\3	1.0	23
SIEMENS	Bl64d\3	1.0	1
SIEMENS	Bl64f\3	1.0	1
SIEMENS	Br62f\3	1.0	1
SIEMENS	Bv40d\3	1.0	1
SIEMENS	I70f\2	1.0	1
SIEMENS	I70f\3	1.0	20
TOSHIBA	FC35	1.0	2

Supplemental Table 2.

Multiple regression results after the exclusion of one significant outlier, showing associations for independent participant characteristics as predictor variables for dependent variables of total mucus plug number and total mucus plug volume.

Variable	Model: No. of Plugs Coefficient	Model Sig.	Model: Mucus Volume Coefficient	Model Sig.
Constant	36.401	.001	2.024	.050
Age	.150	.237	.012	.296
Eosinophils	-.199	.975	-.012	.984
FEV_1%	-.459	**< .001**	-.030	**.003**
Pseudomonas	16.527	**< .001**	1.408	**.001**
Exac 1 vs. 0	1.116	.813	.061	.889
Exac ≥2 vs 0	15.344	**.005**	1.405	**.006**
mMRC 1 vs 0	-7.502	.139	-.398	.394
mMRC ≥2 vs 0	-14.557	**.014**	-.559	.296

Supplemental Table 3 a-e.

These tables provide an analysis comparing bronchial artery (BA) measures between proximal airway generations (G_{1-3}) and the primary analysis (G_{1-6}). The correlations (Rho) and confidence intervals (CI) are reported for each BA parameter. Additionally, the relationship between G_{1-3} BA parameters and clinical measures, including FEV_1 % predicted, FEV_1/FVC, continuous blood eosinophil counts, eosinophils ≥0.3 × 10^9, bronchiectasis severity indices (BSI and FACED), and regression model coefficients for predictors of BA parameters are reported, as in the primary analysis. For subsegmental generations 1-3, 7077 BA pairs were measured, representing 56.5% (7077/12,528) of the total BA pairs, compared to 93.7% (11,709/12,528) for generations 1-6.

a. Correlation of BA measures (G1-3 vs. G1-6).

Parameter		Rho	CI
B_{wt}/A G_{1-3}	B_{wt}/A G_{1-6}	.972	(.955, .983)
B_{wa}/B_{oa} G_{1-3}	B_{wa}/B_{oa} G_{1-6}	.979	(.966, .987)
B_{in}/A G_{1-3}	B_{in}/A G_{1-6}	.988	(.981, .993)

b. Correlation of BA G1-3 measures with FEV1 and FEV1/FVC.

Parameter	FEV_1 % predicted	FEV_1 % predicted	FEV_1/FVC	FEV_1/FVC
	Rho	CI	Rho	CI
B_{wt}/A G_{1-3}	-.580	(-.724, -.389)	-.501	(-.666 -.289)
B_{wa}/B_{oa} G_{1-3}	-.581	(-.724, -.389)	-.534	(-.690, -.330)
B_{in}/A G_{1-3}	.297	(.053, .507)	.338	(.099, .541)

c. Correlation of BA G1-3 measures with eosinophils (continuous and binary).

Parameter	Continuous Eosinophils		Eosinophils Ever ≥0.3*10^9	
	Rho (Spearman)	CI	r (point bi-serial)	CI
B_{wt}/A G_{1-3}	-.027	(-.273, .222)	.059	(-.192, .302)
B_{wa}/B_{oa} G_{1-3}	.101	(-.150, .341)	0.135	(-.116, .371)
B_{in}/A G_{1-3}	-.165	(-.397, .086)	-0.174	(-.404, .077)

d. Correlation of BA G1-3 measures with BSI and FACED scores.

Parameter	BSI		FACED	
	Rho	CI	Rho	CI
B_{wt}/A G_{1-3}	.470	(.252, .643)	0.410	(.181, .597)
B_{wa}/B_{oa} G_{1-3}	.313	(.070, .520)	0.275	(.029, .490)
B_{in}/A G_{1-3}	.036	(-.214, .281)	.044	(-.206, .289)

e. Multivariate regression for predictors of BA measures G1-3.

Variable	Model: B_{wt}/A G_{1-3} Coeff.	Model Sig.	Model: B_{wa}/B_{oa} G_{1-3} Coeff.	Model Sig.
Constant	.216	<.001	.595	< .001
Age	<.001	.746	-.001	.273
Eosinophils	-.013	.377	.019	.589
FEV_1%	-.001	**<.001**	-.002	**<.001**
Pseudomonas	.033	**.003**	.067	**.009**
Exac 1 vs. 0	-.005	.660	.002	.932
Exac ≥2 vs. 0	.031	**.018**	.059	.058
mMRC 1 vs. 0	-.003	.804	-.012	.673
mMRC ≥2 vs. 0	-.014	.298	-.008	.800

Chapter 6

Association Between Automatic AI-Based Quantification of Airway-Occlusive Mucus Plugs and All-Cause Mortality in Patients with COPD

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Abstract

In this cohort study involving 9,399 current and former smokers from the COPDGene study, we assessed the relationship between AI-quantified mucus plugs on chest CTs and all-cause mortality. Our results revealed a significant positive association, particularly for those with COPD GOLD stages 1-4, with hazard ratios of 1.18 for 1-2 mucus-obstructed bronchial segments and 1.27 for ≥3 obstructed segments. This corroborates previous visual mucus plug counting research and demonstrates the relevance of mucus plugs in COPD pathology and as a marker for risk assessment. Automated mucus plug quantification methods may provide an efficient tool for both clinical evaluations and research.

Introduction

Chronic obstructive pulmonary disease (COPD) affects millions worldwide, ranking as a leading cause of mortality.[1] Central to COPD pathology is mucociliary dysfunction, leading to mucus plugs that can occlude the airways.[2] Mucus plugs, detectable in CT scans of many COPD patients, are linked to several adverse outcomes, including impaired airflow, lower oxygen levels, and reduced exercise tolerance.[3] Furthermore, mucus plugs can persist for years without symptoms like cough or sputum production.[4] Finally, the presence of mucus plugs in medium- to large-sized airways has been associated with all-cause mortality in COPD (GOLD 1-4), through meticulous visual counting of the number of mucus-obstructed bronchial segments.[5] The investigation was carried out on a subset of the data from the Genetic Epidemiology of COPD (COPDGene) study.[6]

Our study employed an artificial intelligence (AI) based platform (LungQ) for automated mucus quantification on chest CT scans to explore its association with mortality in the full cohort of all Phase 1 COPDGene participants, across all COPD stages including GOLD 0 and PRISm. We hypothesized that automated quantification would confirm visual scoring findings and would provide enhanced detail and efficiency in assessing the prognostic significance of mucus plugs in COPD.

Methods

COPDGene is a multicenter, prospective study on COPD genetics and epidemiology. It enrolled non-Hispanic Black and White participants aged 45-80 with a significant smoking history (≥10 pack-years). Exclusion criteria and ethical considerations have been outlined in the original COPDGene protocol.[5] The study included 10198 (ex-) smokers, enrolled from November 2007 to April 2011, followed up at 5 and 10 years. Data collection involved questionnaires, spirometry, and standardized chest CT scans using <1mm slice protocols. Mortality, spirometry and demographic data were sourced from the COPDGene database.

For our study all 10198 Phase 1 ever-smoker participants were included in the analysis. Meaning that COPD GOLD stage 1-4, GOLD 0, and PRISm were all included.[7]

Automatic mucus plug quantification was performed using the LungQ platform (Thirona, Nijmegen, The Netherlands). LungQ uses AI-based algorithms to segment the bronchial tree and identify each bronchopulmonary segment. Mucus plugs are detected throughout the lung and linked to their respective segments. The detection

algorithm, trained on expert annotations, identifies full mucus obstructions with clear proximal and distal airways, providing both location and volumetric assessments. The segmentation combines seed-based and voxel-based methods, providing accurate detection and quantification of mucus plugs along the entire bronchi, including the peripheries. (Figure 1a)

Participants were categorized by the number of mucus-obstructed standard bronchopulmonary segments: 0, 1-2, or ≥3. Emphysema percentage was based on the lung parenchyma with attenuation below –950 Hounsfield Units (-950HU%) and airway wall thickness by taking the square root of the wall area for a hypothetical airway with a 10-mm inner perimeter (Pi10).[8]

Cox proportional hazard regression assessed the relationship between mucus plug scores categories and mortality in three models as in the study by Diaz et al.[5] The first model adjusted for demographics, smoking history, FEV_1, emphysema and Pi10. The second added coronary disease, chronic bronchitis, asthma, and annual exacerbations. The third model consisted of the first model plus the BODE index, the most validated COPD mortality prediction score.[9] Analyses, performed using R (4.3.2), considered p-values <.05 significant without adjustment for multiple testing.

Results

The final cohort for analysis consisted of 9399 participants, after exclusion of 799 participants due to missing CT scans (n=297), poor-quality CT scans (n=82), technical issues (n=360), or missing spirometry data (n=60). In total 4165 participants had COPD GOLD 1-4 and 5234 participants GOLD 0 and PRISm. Over a median follow-up of 3957 days there were 2633 (28.0%) deaths. Of all participants, 7200 (76.6%) participants had a score of 0, indicating no mucus-obstructed segments, 1535 (16.3%) had 1-2, and 664 (7.1%) had 3 or more mucus-obstructed segments. See Table 1 for participant characteristics and Figure 1b and 1c for mucus plug distribution across GOLD stages.

In the adjusted model, automated mucus plug score categories were significantly associated with all-cause mortality. Hazard ratios (HR) were 1.14 (CI: 1.03-1.26) for 1-2 mucus-obstructed segments and 1.24 (CI: 1.09-1.42) for 3 or more. In the second model adjusted for additional confounders HR 1.13 (CI: 1.02-1.25) and HR 1.21 (CI: 1.06-1.38). In the third model adjusting for the BODE index, hazard ratios were 1.10 (CI: 0.995-1.22) and 1.15 (CI: 1.0-1.31), respectively. See Table 2.

Table 1. Participant characteristics

Complete Phase 1 cohort (n=9399)	**Mucus plug score category** (No. of segments w/ mucus plugs)		
Characteristic	0 (n=7200)	1-2 (n=1535)	≥3 (n=664)
Age, median (IQR), y	57.7 (51.3-65.1)	62.3 (54.5-69.0)	64.4 (57.1-70.7)
Sex			
Female	47.6%	44.7%	39.5%
Male	52.4%	55.3%	60.5%
Race and ethnicity			
Non-Hispanic White	4733 (64.3%)	1173 (75.8%)	540 (81.2%)
Non-Hispanic African American	2618 (35.7%)	376 (24.2%)	125 (18.8%)
BMI, median (IQR)	28.3 (24.7-32.6)	27.1 (23.5-31.5)	25.5 (22.3-29.4)
Current smoker, No. (%) [No.]	3901 (54.2%)	747 (48.7%)	291 (43.8%)
Pack-years of smoking, median (IQR)	37.6 (25.9-51.7)	44.0 (32.5-63.3)	47.4 (34.7-68.3)
Medical history			
Chronic bronchitis	1143 (15.9%)	414 (27.0%)	230 (34.6%)
Coronary artery disease	754 (10.5%)	197 (12.8%)	85 (12.8%)
Asthma	760 (11.4%)	247 (16.1%)	165 (24.8%)
Exacerbations / year (mean, SD)	0.28 (0.79)	0.58 (1.09)	1.02 (1.50)
COPD GOLD stage of severity			
PRISm	971 (13.5%)	145 (9.4%)	23 (3.5%)
0 (≥10 packyears with FEV_1/FVC>0.7)	3732 (51.8%)	320 (20.8%)	43 (6.5%)
1 (Mild)	613 (8.5%)	115 (7.5%)	21 (3.2%)
2 (Moderate)	1265 (17.6%)	396 (25.8%)	143 (21.5%)
3 (Severe)	478 (6.6%)	359 (23.4%)	237 (35.7%)
4 (Very severe)	141 (2.0%)	200 (13.0%)	197 (29.7%)
BODE index, median (IQR)	0 (0.0-2.0)	2 (0.0-4.0)	4 (2.0-5.0)
FEV_1, L, median (IQR)	2.41 (1.85-3.01)	1.69 (1.09-2.41)	1.16 (0.77-1.71)
FEV_1, % predicted, median (IQR)	85.3 (70.6-97.6)	62.0 (39.9-82.8)	40.5 (27.0-59.2)
Emphysema on CT, median (IQR) , %	1.54 (0.45-4.85)	4.52 (1.05-16.7)	11.33 (2.90-24.15)
Airway wall thickness, median (IQR) , mm	2.14 (1.84-2.53)	2.61 (2.19-3.06)	3.02 (2.58-3.46)
Total number of plugs			
Median (IQR), no.	0.0	1.0 (1.0-2.0)	7.0 (5.0-12.0)
Total plug volume (mm^3)			
Median (IQR)	0 (0-0)	39.8 (14.6-93.7)	318.1 (164.0-742.4)

Table 2. Association Between Mucus Plug Score and All-Cause Mortality

All COPDGene participants		**Mucus plug score** (No. of segments w/ mucus plugs)				
	No.	0 (n =7200)	1-2 (n =1535)		≥3 (n= 664)	
Deceased, n (%)		1625 (22.6%)	638 (41.6%)		371 (55.9%)	
		HR (95% CI)	HR (95% CI)	p-value	HR (95% CI)	p-value
Adjusted model*	9397	Reference	1.14 (1.03-1.26)	0.010	1.24 (1.09-1.42)	0.001
Adjusted model plus coronary artery disease, chronic bronchitis, current asthma and exacerbations per year	9397	Reference	1.13 (1.02-1.25)	0.016	1.21 (1.06-1.38)	0.006
Adjusted model plus BODE index†	9272	Reference	1.10 (0.995-1.221)	0.062	1.15 (1.001-1.312)	0.048

Participants with GOLD stage 1-4		**Mucus plug score** (No. of segments w/ mucus plugs)				
	No.	0 (n= 2497)	1-2 (n= 1070)		≥3 (n= 598)	
Deceased, n (%)		868 (34.8%)	552 (51.6%)		355 (59.4%)	
		HR (95% CI)	HR (95% CI)	p-value	HR (95% CI)	p-value
Adjusted model*	4163	Reference	1.18 (1.05-1.32)	0.005	1.27 (1.10-1.46)	0.001
Adjusted model plus coronary artery disease, chronic bronchitis, current asthma and exacerbations per year	4163	Reference	1.17 (1.04-1.31)	0.008	1.24 (1.07-1.43)	0.004
Adjusted model plus BODE index†	4068	Reference	1.14 (1.02-1.28)	0.027	1.22 (1.05-1.41)	0.008

Particpants with GOLD 0 and PRISm		**Mucus plug score** (No. of segments w/ mucus plugs)				
	No.	0 (n=4703)	1-2 (n=465)		≥3 (n=66)	
Deceased, n (%)		757 (16.1%)	86 (18.5%)		16 (24.2%)	
Adjusted model*	5234	Reference	1.05 (0.83-1.31)	0.692	1.31 (0.79-2.17)	0.303
Adjusted model plus coronary artery disease, chronic bronchitis, current asthma and exacerbations per year	5234	Reference	1.04 (0.83-1.30)	0.754	1.26 (0.76-2.11)	0.372
Adjusted model plus BODE index†	5204	Reference	1.04 (0.83-1.30)	0.738	1.24 (0.75-2.06)	0.412

Cox proportional hazard regression models. *: Adjusted for: age, gender, race, BMI, smoking status, packyears, FEV_1%, emphysema (-950HU%), airway wall thickness (Pi10), scanner model; †: Including all variables from the adjusted model except FEV_1 and BMI plus adjustment for the BODE index (continuous). Proportional hazard assumptions were evaluated using Schoenfeld residuals.

Among 4165 participants with COPD (GOLD stages 1-4), hazard ratios were 1.18 (CI: 1.05-1.32) for 1 or 2 obstructed segments and 1.27 (CI: 1.10-1.46) for 3 or more obstructed segments. In the second model 1.17 (CI: 1.04-1.31) and 1.24 (CI: 1.07-1.43). In the third model 1.14 (CI: 1.02-1.28) and 1.22 (CI: 1.05-1.41), respectively. In COPD stages (GOLD 0 and PRISm), mucus plug scores were lower and showed no significant association with mortality.

Discussion

This study confirms automated mucus plug analysis in the COPDGene cohort associations with higher mortality, consistent with visual scoring methods, even when adjusting for confounders and the BODE-index. Hazard ratios for COPD stages 1-4 subgroup of 1.18 and 1.27, for 1-2 and ≥3 obstructed segments, respectively, were highly similar to those found by visual methods. No mortality association was found in non-COPD subgroups (GOLD 0 and PRISm).

LungQ detected similar mucus plug counts to Diaz et al., with 25.7% (1070/4165) of participants showing 1-2 obstructed segments and 14.4% (598/4165) with ≥3, reflecting both method's identification of mucus plugs in 40% of GOLD 1-4 participants. The variation in the standard bronchopulmonary segment anatomy and the algorithm's conservative design, emphasizing specificity, may account for differences. The prevalence of mucus plugs in GOLD 1-4 is substantially higher than what was observed in the PRISM (14%) and GOLD 0 participants (10%). Furthermore, also substantially higher than what can be observed in never-smokers. In a limited COPDGene control group of 107 never-smokers, LungQ detected mucus plugs in only 6 participants (5.6%), with 4 participants with one plug, 1 participant with three plugs in two segments, and 1 subject with four plugs in four segments (Data on file).

The study's strengths include the inclusion of all COPDGene Phase 1 participants including 5234 participants classified as GOLD 0 and PRISm as control groups, and the consistency of the use of an automated analysis over visual methods. However, one limitation is the absence of direct validation of the automated measurement against visual scoring. Due to the exceptionally laborious nature of visual mucus plug counting, large-cohort comparison is challenging. Therefore, we have focussed on evaluating the association of automated mucus plug score categories with mortality. The observational design is another limitation as it limits causal conclusions.

The three mucus score categories (0, 1-2, and ≥3 obstructed segments) were chosen for their demonstrated stratification of risk.[5] Continuous variables of total mucus

plug numbers and total mucus volume are highly left-skewed, limiting their utility for the current models. The distribution of mucus across segments and quantifying the total number and volume of mucus plugs may add further relevant information, particularly for longitudinal analysis at the individual level. These aspects warrant further exploration in future studies.

Overall, the results across various COPD severities confirm the association of mucus plugs with mortality, likely mediated through inflammation, infection, and ventilation/perfusion mismatch. This underscores their potential as markers of disease severity and may guide treatment interventions. Automated analysis of mucus plugs could identify high-risk subgroups by integrating patient data and mucus metrics, opening new opportunities for personalized risk assessment, research, and therapeutic strategies in COPD.

References

1. Collaborators, G.B.D.C.R.D., *Global burden of chronic respiratory diseases and risk factors, 1990-2019: an update from the Global Burden of Disease Study 2019.* EClinicalMedicine, 2023. **59**: p. 101936.
2. Boucher, R.C., *Muco-Obstructive Lung Diseases.* N Engl J Med, 2019. **380**(20): p. 1941-1953.
3. Dunican, E.M., et al., *Mucus Plugs and Emphysema in the Pathophysiology of Airflow Obstruction and Hypoxemia in Smokers.* Am J Respir Crit Care Med, 2021. **203**(8): p. 957-968.
4. Okajima, Y., et al., *Luminal Plugging on Chest CT Scan: Association With Lung Function, Quality of Life, and COPD Clinical Phenotypes.* Chest, 2020. **158**(1): p. 121-130.
5. Diaz, A.A., et al., *Airway-Occluding Mucus Plugs and Mortality in Patients With Chronic Obstructive Pulmonary Disease.* JAMA, 2023. **329**(21): p. 1832-1839.
6. Regan, E.A., et al., *Genetic epidemiology of COPD (COPDGene) study design.* COPD, 2010. **7**(1): p. 32-43.
7. Agusti, A., et al., *Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD Executive Summary.* Am J Respir Crit Care Med, 2023. **207**(7): p. 819-837.
8. Grydeland, T.B., et al., *Quantitative computed tomography: emphysema and airway wall thickness by sex, age and smoking.* Eur Respir J, 2009. **34**(4): p. 858-65.
9. Celli, B.R., et al., *The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease.* N Engl J Med, 2004. **350**(10): p. 1005-12.

Part II

Treatment and Outcomes

Chapter 7

The Effect of Beclomethasone-Formoterol Versus Placebo on Chronic Cough in Patients with Non-CF Bronchiectasis: The FORZA Randomised-Controlled Trial

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To the Editor,

Bronchiectasis is a chronic inflammatory condition of the airways associated with a high burden of symptoms, including chronic cough.[1] The current cornerstones for the management of bronchiectasis are the identification of aetiology, comorbidity and treatable traits. The benefit of treatment with inhaled corticosteroids (ICS), with or without long-acting beta agonists (LABA), is unclear. Guidelines advise that ICS should only be used in patients with coexisting asthma or COPD, since the indication for ICS or ICS/LABA in bronchiectasis has not been established otherwise.[1,2] On the other hand, early results of an EMBARC (European Multicentre Bronchiectasis Audit and Research Collaboration) registry analysis show that up to 53.1% of bronchiectasis patients use ICS or ICS/LABA, of which one-third do not have a diagnosis of asthma or COPD.[3] We hypothesised that ICS/LABA could reduce complaints of cough in bronchiectasis patients without asthma or COPD. Therefore, we performed a multicentre, randomised, double-blind, placebo-controlled trial comparing beclomethasone-formoterol versus placebo.

The FORZA study (clinicaltrials.gov: NCT03846570) was conducted in three hospitals in the Netherlands. Adult patients with bronchiectasis confirmed by computed tomography according to the Fleischner Society[4] and BTS definition[1] were recruited from outpatient clinics. Patients had to be on a stable treatment regimen and without recent exacerbation (≥6 weeks). Cough had to be present daily ≥8 weeks. No ICS use was allowed ≥4 weeks before screening. The main exclusion criterion was a diagnosis of asthma confirmed by spirometry reversibility and/or bronchial provocation testing, or COPD, according to GINA and GOLD guidelines.[5,6] Current smokers or patients with a history of ≥10 packyears were also excluded. Participants were randomised to use either beclomethasone-formoterol (Fostair®) 200/12 mcg or placebo twice-daily via identical metered-dose aerosol inhalers. The primary endpoint was the change in cough after three months, measured by the Leicester Cough Questionnaire (LCQ), using ≥1.3 points as the minimum clinically important difference.[7] The minimum sample size was 66 patients to provide 80% power to detect a 2.7-point difference in LCQ between treatment groups with a 5% level of significance. Accounting for dropouts, we aimed to enrol 72 participants. Furthermore, we assessed the change in FEV1, mMRC score, Quality of Life-Bronchiectasis (QoL-B) respiratory domain[8], pulmonary exacerbations (PEs; defined as worsening of ≥1symptom[1] and prescription of systemic antibiotics) and adverse events (AEs). We used the one-way analysis of covariance (ANCOVA) to assess differences from baseline to three months between the beclomethasone-formoterol and placebo groups, based on intention-to-treat. The ethics review committee approved the study (approval number NL61630.078.18).

In total 741 patients with diagnostic codes for bronchiectasis were screened for eligibility. The majority was excluded because of a co-diagnosis of asthma, COPD, smoking history or current ICS use. Other reasons for exclusion were nondaily complaints of cough or refusal to participate, especially during the SARS-CoV-2 pandemic. The study was terminated prematurely due to insufficient inclusion.

Thirty-four patients were enrolled between January 2019 and April 2022. Seventeen participants received beclomethasone-formoterol, and seventeen received placebo. For all participants, the mean and standard deviation (SD) age was 53.9 years (18.3) and 64.7% were women. Mean lung function as measured by FEV1% predicted 82.9%(15.8), BMI 23.9 (4.2), former smoking packyears 3.8 (3.3). Seven patients had chronic *Pseudomonas aeruginosa* infection. The mean LCQ score was 15.9 (2.7), QoL-B respiratory 62.7 (21.5), and mMRC score 1.3 (0.9). The mean number of PEs in the previous year was 1.1 (1.3). FACED bronchiectasis severity score was 1.2 (1.2). No significant differences were observed at baseline between the two groups. (Table)

After three months, both treatment groups showed no difference in LCQ scores after controlling for baseline scores, β=-.312,p=.708. Furthermore, after controlling for baseline scores, no effect of treatment was found on the QoL-B respiratory scores (β =3.905,p=.538), mMRC scores (β=-.011,p=.978) and the FEV1%predicted (β=2.175,p=.264). (Table)

PEs occurred in 4/17 (23.5%) patients in the beclomethasone-formoterol group vs 1/17 (5.8%) patients in the placebo group. The number of patients with AEs (including PEs) in the beclomethasone-formoterol group was 11/17 (64.7%) versus 5/17 (29.4%) in the placebo group, X^2 (1,n=34, 4.25,p=0.039). Oropharyngeal symptoms (e.g., hoarseness, sore throat, and oral candida) were the most frequent AEs. In the beclomethasone-formoterol group, 4/17 (23.5%) patients discontinued the study medication due to AEs, versus 1/17 (5.8%) in the placebo group.

To date, this is the only randomised, double-blind, placebo-controlled trial to investigate ICS/LABA in bronchiectasis patients with strict exclusion of patients with asthma and COPD. We found no treatment effect on cough, nor change in quality of life, dyspnoea, lung function or PEs. However, there were significantly more AEs in the ICS/LABA group.

Unfortunately, the SARS-CoV-2 pandemic severely impacted participant inclusion. Still, despite incomplete statistical power and recruiting a patient population with a relatively mild clinical profile (e.g. high LCQ and low FACED scores), the lack of

benefit of beclomethasone-formoterol and the occurrence of more AEs is a relevant outcome.

There has been only one other trial investigating ICS/LABA in bronchiectasis. In a double-blind comparison of high-dose budesonide vs medium-dose budesonide-formoterol, the authors reported symptomatic benefits of ICS/LABA, concluding that adding LABA could help reduce ICS dose.[9] However, there was no comparison with placebo thus inadequate to determine the particular benefit of ICS or ICS/LABA. A Cochrane review of 2018 showed that there is insufficient evidence to support the use of ICS in adults with steady-state bronchiectasis.[10] Subsequent studies indicated a negative impact of ICS use. In the early presented data of an upcoming EMBARC publication, ICS use is associated with an increased exacerbation and hospitalisation risk.[3] Another prospective study of 264 patients found an association of ICS use with increased morbidity as well as all-cause mortality, also after adjusting for age, sex, FEV1 and concomitant asthma/COPD.[11]

Bronchiectasis can be associated with nonspecific bronchial hyperreactivity, which is explained by decreased baseline airway calibre and epithelial inflammation resulting in an increased airway smooth muscle tone.[12] Remarkably, we found that about 30% of the potential participants without a history of asthma were ineligible due to new-found significant reversibility or positive bronchial provocation test.[13] Therefore, we recommend to assess bronchodilator responsiveness and/or bronchial hyperreactivity in all bronchiectasis patients when considering ICS and/or bronchodilators.

In asthma and COPD, high blood eosinophil counts may predict ICS effectiveness. It can be hypothesized that patients with bronchiectasis with an eosinophilic phenotype also benefit from ICS. A recent large cohort study demonstrated that increased eosinophils (>300 cells·μL) were present in ~20% of bronchiectasis patients and that these represented a distinct subtype.[14] In a study with patients with stable bronchiectasis, beneficial effects were found from using inhaled fluticasone when eosinophils ≥150 cells·μL / ≥3% were present, in terms of quality of life and a trend towards decreased exacerbations.[15] However, this was a post-hoc analysis of an uncontrolled trial and a lower eosinophil cut-off than the mentioned study by Shoemark et al.[14] There are still no prospective controlled studies investigating the effect of ICS on bronchiectasis patients with increased eosinophils. In our study, an analysis according to eosinophil counts was not pre-specified and subgroups were too small for post-hoc analysis.

To conclude, the use of ICS/LABA in patients with bronchiectasis, without asthma or COPD, did not result in a decrease in cough or other benefits. However, the occurrence

of significantly more adverse events warrants caution for the prescription of ICS/LABA in the absence of asthma or COPD.

Baseline characteristics				
Variable		Placebo	Beclomethasone-formoterol	*p*-value
		n=17	n=17	
Age (mean, SD)		56 (18)	52 (19)	0.467 *
Gender (n, %)	Female	12 (70.6%)	10 (58.8%)	0.721 †
Etnicity (n, %)	Caucasian	16 (94.4%)	14 (87.5%)	0.601 †
BMI (mean, SD)		24.8 (4.6)	23 (3.7)	0.226 *
Smoking status (n, %)	Never	13 (76.5%)	12 (70.6%)	1 †
	Former	4 (23.5%)	5 (29.4%)	
Packyears (mean, SD)		1.5 (1)	5.6 (3.4)	0.053 *
Aetiology (n, %)	Idiopathic	2 (11.8%)	8 (47%)	0.032 †
	Post-infective	4 (23.5%)	1 (5.9%)	
	Immunodef	0	4 (23.5%)	
	PCD	2 (11.8%)	1 (5.9%)	
	Other	9 (52.9%)	3 (17.6%)	
Chronic azithromycin use (n, %)		8 (47.1%)	8 (47.1%)	1 †
Eosinophil count (*10^9/L) (mean, SD)		0.18 (0.14)	0.12 (0.09)	0.155 *
FEV1 (L) (mean, SD)		2.63 (0.89)	2.56 (0.88)	0.819 *
FEV1 % predicted (mean, SD)		86.5 (13.3)	79.3 (17.6)	0.186 *
LCQ score (mean, SD)		16.2 (2.7)	15.2 (3.5)	0.366 *
QoL-B respiratory (mean, SD)		68.5 (13.3)	65.9 (13.6)	0.588 *
mMRC (mean, SD)		1.24 (0.9)	1.41 (0.93)	0.581 *
PEs past 12 months (mean, SD)		0.65 (0.93)	1.56 (1.46)	0.211 ‡
F (FEV1 ≥50%) (n, %)		17 (100%)	17 (100%)	1 †
A (age ≥70 years) (n, %)		3 (17.6%)	3 (17.6%)	1 †
C (colonization with Pseudomonas) (n, %)		2 (11.8%)	3 (17.6%)	1 †
E (>2 lobes affected) (n, %)		10 (58.8%)	9 (52.9%)	1 †
D (mMRC >2) (n, %)		1 (5.9%)	4 (23.5%)	0.335 †
FACED score (mean, SD)		1.12 (1.17)	1.29 (1.36)	0.687 *

	Outcomes		*p*-value
Variable	Placebo	Beclomethasone/ formoterol	
	n=17	n=17	
LCQ score after 1 month (mean, SD)	16.8 (3.0)	16.4 (2.4)	
LCQ score after 3 months (mean, SD)	16.6 (3.3)	16.2 (3.5)	0.708 §
QoL-B respiratoy score after 1 month (mean, SD)	67.9 (16.6)	69.4 (13.0)	
QoL-B respiratory score after 3 months (mean, SD)	67.5 (16.5)	71.4 (18.6)	0.538 §
FEV1 %predicated after 1 month (mean, SD)	89.1 (17.7)	78.8 (21.9)	
FEV1%predicted after 3 months (mean, SD)	86.5 (14.0)	81.8 (21.6)	0.264 §
mMRC score after 1 month (mean, SD)	1.46 (1.05)	1.2 (1.03)	
mMRC score after 3 months (mean, SD)	1.25 (1.29	1.2 (0.92)	0.978 §
Pulmonary exacerbations (PEs) during study period (n)	1	4	0.146 †
Adverse events (including PE) during study period (n)	5	11	0.039 †
Discontinuation of study drug due to AEs (n)	1	4	0.146 †
Adverse events (without PEs) (n)			
Oropharyngeal symptoms (hoarseness, oral candidiasis, sore throat)	1	3	
Muscle cramps		1	
Restlessness, palpitations	1	1	
Urinary tract infection	1		
Abdominal discomfort	1		
Subretinal edema		1	
Gastroesophageal reflux		1	

*: t-test; †:chi-squared; ‡: median, non-parametric; §: ANCOVA for treatment effect after controlling for baseline

References

1. Hill AT, Sullivan AL, Chalmers JD et al. British Thoracic Society Guideline for Bronchiectasis in Adults. Thorax 2019;74(Suppl 1):1–69. doi:10.1136/thoraxjnl-2018-212463
2. Polverino E, Goeminne PC, McDonnell MJ, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. *European Respiratory Journal.* 017;50(3):1700629.
3. Polverino E, Chalmers JD, Aliberti S, et al. Inhaled corticosteroids use in patients with bronchiectasis: Data from the EMBARC registry. *European Respiratory Journal* 2021;58 (suppl 65) DOI**:** 10.1183/13993003.congress-2021.OA1312
4. Hansel DM, Bankier AA, MacMahon H, et al. Fleischner Society: Glossary of Terms for Thoracic Imaging. Radiology. 2008 Mar;246(3):697-722. doi: 10.1148/radiol.2462070712. Epub 2008 Jan 14.
5. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2018. Available from: www.ginasthma.org
6. GOLD: Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018.2018. Available from: https://goldcopd.org
7. Raj AA, Pavord DI, Birring SS. Clinical Cough IV: What is the Minimal Important Difference for the Leicester Cough Questionnaire? In: Chung KF, Widdicombe J, eds. *Pharmacology and Therapeutics of Cough*. Berlin, Heidelberg: Springer Berlin Heidelberg; 2009:311-320.
8. Quittner AL, O'Donnell AE, Salathe MA, et al. Quality of Life Questionnaire-Bronchiectasis: final psychometric analyses and determination of minimal important difference scores. *Thorax.* 2015;70(1):12-20.
9. Martínez-García MÁ, Soler-Cataluña JJ, Catalán-Serra P, et al. Clinical efficacy and safety of budesonide-formoterol in non-cystic fibrosis bronchiectasis. Chest. 2012 Feb;141(2):461-468
10. Kapur N, Petsky HL, Bell S, et al. Inhaled corticosteroids for bronchiectasis. Cochrane Database Syst Rev. 2018 May 16;5(5):CD000996. doi: 10.1002/14651858.CD000996.pub3. PMID: 29766487; PMCID: PMC6494510.
11. Håkansson KEJ, Fjaellegaard K, Browatzki A et al. Inhaled Corticosteroid Therapy in Bronchiectasis is Associated with All-Cause Mortality: A Prospective Cohort Study. Int J Chron Obstruct Pulmon Dis. 2021 Jul 16;16:2119-2127. doi: 10.2147/COPD.S311236.
12. Ip M, Lam WK, So SY et al. Analysis of factors associated with bronchial hyperreactivity to methacholine in bronchiectasis. Lung. 1991;169(1):43-51. doi: 10.1007/BF02714140.
13. De Koning Gans M, Kamphuis LSJ, Hoek RAS, et al. European Respiratory Journal Sep 2019, 54 (suppl 63) OA4944; DOI: 10.1183/13993003.congress-2019.OA4944
14. Shoemark A, Shteinberg M, Soyza AD, et al. Characterization of Eosinophilic Bronchiectasis: A European Multicohort Study. *American journal of respiratory and critical care medicine.* 2022;205(8):894-902.
15. Aliberti S, Sotgiu G, Blasi F, Saderi L, Posadas T, Martinez Garcia MA. Blood eosinophils predict inhaled fluticasone response in bronchiectasis. *European Respiratory Journal.* 2020;56(2):2000453.

Chapter 8

Reduced Exacerbation Frequency and Prednisone Dose in Patients with ABPA and Asthma Treated with Dupilumab prednisone dose in patients with ABPA and asthma treated with dupilumab

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To the Editor,

We present a series of seven patients with allergic bronchopulmonary aspergillosis (ABPA) and asthma who were treated with dupilumab, a promising novel therapeutic option for ABPA.

ABPA is a difficult-to-treat disease caused by airway inflammation triggered by an excessive allergic response to inhaled fungal spores. ABPA typically occurs in patients with asthma or cystic fibrosis and is characterized by dyspnea, cough, mucus plugs and frequent exacerbations and is associated with bronchiectasis. High serum IgE levels and high eosinophil counts are key biomarkers in patients with ABPA. The cornerstones of treatment have been systemic steroids and azole antifungals, but treatment protocols have never been investigated extensively. As these drugs often carry harmful side-effects, it is crucial to find alternative treatments.[1]

Dupilumab is an interleukin(IL)-4 alpha receptor antagonist impeding IL-4 and IL-13 signaling, broadly inhibiting type 2 inflammation by counteracting IgE producing B-cells and eosinophils.[2] This gives dupilumab a rational mechanism of action in ABPA. Dupilumab efficacy in patients with ABPA and asthma has previously been reported in incidental patients.[3-4] Interestingly, a post-hoc analysis of the LIBERTY trial also showed reduced exacerbations in participants with serologic markers suggestive of ABPA.[5]

Our retrospective case series approved by the institutional review board presents seven patients with ABPA (International Society for Human and Animal Mycology diagnostic criteria [1]) and allergic asthma who had received between 4 and 21 months of dupilumab treatment. All patients provided informed consent. Their FEV1, steroid dose and total IgE levels as well as the number of exacerbations were compared between baseline and six months prior to first administration of dupilumab *versus* six months after start of dupilumab treatment.

Six males and one female were included, mean age 71 years. All patients had a diagnosis of ABPA for ≥1 year. All patients were on maintenance prednisone at baseline. All patients used inhaled corticosteroids and bronchodilators. Six patients had a history of azole treatment. Median FEV1 at baseline was 84% predicted (27-96%) and median total IgE was 1841 kU/L (66-4147 kU/L). Baseline serum eosinophils were generally absent, likely due to steroid therapy.

All patients started dupilumab between March 2019 and July 2020, maintenance dose 300 mg every two weeks.

During the six months after start of dupilumab, the number of exacerbations for which additional courses of steroids were prescribed was significantly lower in all patients at mean 0.29 (SD 1.13) exacerbations, *versus* 2.43 (SD 0.49) exacerbations in the six months before dupilumab (paired t-test, $t(6)=5.3$, $p<0.05$). After six months of treatment, maintenance prednisone was discontinued or reduced in all patients, with mean steroid dose at baseline 9.17 mg/day (SD 1.3) *versus* 2.1 mg/day (SD 2.46) after six months (paired t-test, $t(5)=5.94$, $p<0.05$). Four patients had a ≥10%. increase in predicted FEV1. Four patients had a documented reduction in total IgE. (See Table 1)

Reported side-effects were fatigue in one patient and arthralgia in another patient, which caused the latter to discontinue treatment. One patient experienced steroid withdrawal syndrome during steroid tapering.

This is the largest reported case series of dupilumab treatment for ABPA patients. As in previous smaller reports, our findings indicate that dupilumab has strong effects on both clinical and biochemical parameters, most importantly the number of exacerbations and maintenance steroid dose. Side-effects were limited, as was also reported in larger real-world studies.[6]

These results are naturally limited by retrospective methods and the small number of patients, but results from a prospective trial are not expected until 2023 (Clinicaltrials.gov NCT04442269). Until then, based on real-world experiences and strong immunological arguments, dupilumab is a very promising new agent that can already be considered for empiric treatment of patients with ABPA and asthma.

Table 1. Patients characteristics and parameters at baseline, before and after starting dupilmab treatment

	Baseline and before dupilumab				Six months after starting dupilumab			
Patient Sex, age	FEV1 %pred	Prednison maintenance dose (mg/d)	Total IgE kU/L	No. exacerbations / six months before dupilumab	FEV1 %pred	Prednison maintenance dose (mg/d)	Total IgE kU/L	No. exacerbations / six months after starting dupilumab
1. M,74	96	7.5	2324	3	106	0	*	0
2. F, 78	68	10	>2000	2	68	5	*	1
3. M, 69	69	7.5	66	1	88	5	*	0
4. M, 83	84	10	1841	3	103	0	913	0
5. M, 78	92	10	4147	1	94	2.5	651	0
6. M, 61	27	No stable dose due to frequent exacerbations	1046	4	26	0	531	1
7. M, 52	95	10	994	3	109	0	474	0

*Incomplete data

References

1. Agarwal R, Chakrabarti A, Shah A, et al. Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria. Clin Exp Allergy. 2013 Aug;43(8):850-73. doi: 10.1111/cea.12141.
2. Le Floc'h A, Allinne J, Nagashima K, et al. Dual blockade of IL-4 and IL-13 with dupilumab, an IL-4Rα antibody, is required to broadly inhibit type 2 inflammation. Allergy 2020 May;75(5):1188-1204. doi: 10.1111/all.14151.
3. Ramonell RP, Lee FE, Swenson C, Kuruvilla M. Dupilumab treatment for allergic bronchopulmonary aspergillosis: A case series. J Allergy Clin Immunol Pract. 2020 Feb;8(2):742-743. doi: 10.1016/j.jaip.2019.11.031.
4. Mümmler C, Kemmerich B, Behr J, Kneidinger N, Milger K. Differential response to biologics in a patient with severe asthma and ABPA: a role for dupilumab? Allergy Asthma Clin Immunol. 2020 Jun 26;16:55. doi: 10.1186/s13223-020-00454-w.
5. Corren J, Sher L, Zhu X, et al. Dupilumab efficacy in patients with uncontrolled, moderate-to-severe allergic bronchopulmonary aspergillosis [Abstract only]. Ann Allergy, Asthma Immunol 2019;123:S15. doi: https://doi.org/10.1016/j.anai.2019.08.071.
6. Nowsheen S, Darveaux JI. Real-world efficacy and safety of dupilumab use in the treatment of asthma [Letter]. Ann Allergy Asthma Immunol. 2021 Jul;127(1):147-149. doi: 10.1016/j.anai.2021.04.011. Epub 2021 Apr 10.

Chapter 9

General Discussion

Discussion

As for his case, the optical and acoustical results corresponded as precisely as one could ever demand of science. Both the old spots and the fresh one had been visible, and there were "strands" that ran from the bronchi well down into the lung itself—"strands with nodules." He would be able to verify that for himself on the X-ray plate.

(*Der Zauberberg*, Thomas Mann 1924)

From Radiological Strands to Modern Medicine: Uncovering Bronchiectasis

Bronchiectasis disease is a chronic respiratory condition characterized by irreversible dilation of the bronchi, airway inflammation, mucus obstruction and recurrent infections, accompanied by cough, sputum and often progressive lung damage. Historically linked to tuberculosis, bronchiectasis remains a significant clinical burden despite advances in respiratory medicine, and has for a long time remained a neglected disease. There remains a severe lack of treatments specifically developed and approved for bronchiectasis and the traditional, qualitative methods of chest CT assessment of bronchiectasis and related changes have not changed for decades. [1, 2] Alongside the often overlapping conditions of asthma and chronic obstructive pulmonary disease (COPD), bronchiectasis represents a major challenge in respiratory medicine, necessitating improved diagnostic tools and more personalized management approaches. [3-5]

High-resolution computed tomography (HRCT) and the arrival of artificial intelligence (AI)-based automated quantitative image analysis offers an opportunity to address this challenge. These technologies enable precise identification and quantification of relevant structural lung abnormalities, enabling disease monitoring and providing insights into disease mechanisms, particularly when combined with clinical data such as lung function, sputum cultures, blood markers and patient outcomes.

Furthermore, research in the past decade has increased our understanding of overlapping inflammatory mechanisms across chronic airway diseases. Distinct endotypes, including neutrophilic and eosinophilic inflammation, provide a common framework for understanding bronchiectasis, asthma, and COPD. However, the link between these inflammatory pathways and structural lung abnormalities remains poorly understood.

This Thesis

This thesis investigated two key strategies to improve the management of bronchiectasis, asthma, and COPD: advanced imaging technologies for better disease phenotyping and targeted anti-inflammatory therapies to improve clinical outcomes. Together, these parts show a hopeful direction to manage these chronic airway diseases.

Part 1: AI-Enhanced Radiological Phenotyping

The first part of this thesis focused on the application of advanced radiological methods to better understand bronchiectasis and its overlap with asthma and COPD. High-resolution computed tomography (HRCT) and automated imaging techniques are used to quantify structural lung abnormalities such as bronchial dilation, wall thickening, and mucus plugging. These methods were shown to correlate with a validated manual scoring system, but provided more detailed and objective data as well as being much less labor-intensive. (Ch. 3 & 4)

The work has highlighted the heterogeneity of bronchiectasis, with CT structural abnormalities varying significantly (from 0-88%) across a large clinical cohort. (Ch. 2 & 4) This heterogeneity underscores the complexity of the disease, suggesting that individual patients with more severe disease are at higher risk for negative outcomes and would benefit from tailored assessments and treatments. Automated analyses, such as the Bronchus-Artery (BA) method, a technique that assesses the ratio of bronchial wall thickness to the accompanying pulmonary artery diameter, were shown to correlate strongly with clinical outcomes, including spirometry, chronic infection, and exacerbation frequency. (Ch. 4 & 5) Additionally, mucus plugging is identified as a significant marker correlating with exacerbations and mortality not only in bronchiectasis but also in asthma and COPD. (Ch. 5 & 6) These findings highlight the potential of AI-driven radiological assessments to enhance disease monitoring, improve patient phenotyping, and facilitate personalized management.

However, to fully realize the clinical impact of these tools, further research is needed to determine which automated metrics offer the most value and to validate their use across diverse patient populations. A critical next step will be the integration of AI-based analysis into routine clinical workflows, such as adding these tools to existing PACS (Picture Archiving and Communication Systems). This integration would enable direct automated evaluation of CT scans, making quantitative data on metrics such as bronchial wall thickness and mucus plugging readily accessible to clinicians, ultimately changing how bronchiectasis and other airway diseases are diagnosed, monitored, and treated, leading to more personalized and effective patient care.

Part 2: Personalizing Bronchiectasis Management: From Steroids to Biologics

The second part of this thesis explored the application of anti-inflammatory therapies in bronchiectasis patients, drawing from treatments used in asthma and COPD. Inhaled corticosteroids (ICS) and long-acting beta-agonists (LABA), the cornerstone therapies for asthma, are evaluated for their efficacy in reducing cough symptoms in bronchiectasis patients without asthma or COPD. (Ch. 7) This lack of effectiveness is likely due to the growing body of evidence suggesting that the benefits of ICS therapy are predominantly seen in patients with eosinophilic inflammation. These results highlight the critical importance of identifying and targeting specific inflammatory endotypes to optimize treatment strategies in bronchiectasis.

In contrast, biological therapies targeting type 2 (T2) driven inflammation, such as dupilumab, show promise in patients with allergic bronchopulmonary aspergillosis (ABPA). In this thesis, dupilumab reduced exacerbations and oral corticosteroid (OCS) dependency in a case series, illustrating the potential of biologicals to address eosinophilic inflammation in selected bronchiectasis phenotypes. (Ch. 8) These findings show the importance of inflammatory endotypes to guide management. Future therapies, including those targeting neutrophilic inflammation, offer additional opportunities to improve outcomes for patients with inflammatory airway diseases.

The Unmet Need for Radiological Quantification

Bronchiectasis disease is characterized by the presence of radiological abnormalities, but currently, the extent of radiological disease is not objectively quantified, nor routinely considered when evaluating a patient's phenotype or assessing their risk of poor outcomes. In routine clinical practice, airway abnormalities are evaluated subjectively on chest radiographs and/or chest CTs without quantification of relevant structural changes related to airway disease such as bronchial widening (bronchiectasis), bronchial wall thickening (a surrogate for inflammation and/or remodeling) or mucus plugging. Only very limited mention of the nature or extent of radiological disease is found in either Dutch or European guidelines.[6, 7] This is remarkable, as many studies have linked radiological markers of bronchiectasis, airway wall thickness and mucus plugs directly to other disease characteristics and outcomes. Only a very rough measure of the extent of disease ('≥3 affected lobes') has been included in the multiple-item FACED and BSI scores for bronchiectasis severity.[8]

From Manual Scores to Automation

However, despite the very limited consideration for the radiological extent of disease, there have been studies that have shown significant correlations between manual scoring and clinical outcomes in bronchiectasis. Despite a strong lack of uniformity, scoring systems for bronchiectasis, such as the Bhalla score, Brody score, and its upgraded version the CF-CT scoring system do provide insights into disease severity and patient prognosis. The Bhalla score correlates well with disease severity markers in bronchiectasis, including FEV_1, sputum purulence, and hospital admissions, as well as already demonstrating a relationship between changes in mucus plugging and changes in FEV_1.[9] The CF-CT score has high reproducibility, which could make it reliable for longitudinal studies.[10] The simplified Reiff score is quicker and easier to use in clinical practice.[11] Despite their utility, these scoring methods have not been widely adopted. Their laborious and time-consuming nature, such as the 12–15 minutes required to score a single chest CT using the Bhalla method, is a significant limitation.[9] More importantly, radiological features like bronchial wall thickening and mucus plugging have hardly been investigated as treatment targets, and they have yet to be established as clinical endpoints in therapeutic trials.

One of the best-validated visual scoring systems for bronchiectasis disease is the Bronchiectasis Scoring Technique for CT (BEST-CT), which was developed based upon a validated morphometry-based scoring method to quantify structural lung damage in paediatric patients with cystic fibrosis (PRAGMA-CF).[12] BEST-CT was shown to be a reproducible quantitative scoring system to phenotype and measure the severity and extent of the structural lung abnormalities in bronchiectasis patients.[13] Disadvantages of the BEST-CT system are that it requires on average two weeks training of the observer, and that it is time consuming, taking up to 45 minutes to score one CT scan. While these factors may be acceptable in research settings where accuracy and reproducibility are prioritized, it forms an important barrier to implementation in clinical practice

The manual scoring of CT features in asthma and COPD, increased airway wall thickness, was associated with higher airway resistance in COPD and air trapping in asthma, indicating its contribution to airflow obstruction and disease severity.[14] Bronchial wall thickening correlated with exacerbation frequency and sputum volume in bronchiectasis patients, highlighting its role in predicting disease severity.[15] Serial changes in CT scores for mucus plugging correlated with pulmonary function fluctuations, with bronchial wall thickness being the primary determinant of significant functional decline.[16] Mucus plugs are common in severe asthma and associated with increased airway eosinophils, suggesting that mucus plugs play a significant role in

chronic airflow obstruction in severe asthma.[17] In COPD patients, manually scored mucus plugs are highly prevalent and significantly associated with higher all-cause mortality, with an adjusted hazard ratio of death of 1.15 for 1 to 2 lung segments and 1.24 for 3 or more segments.[18]

Regarding the actual definition of bronchiectasis, Meerburg et al. conducted a systematic review to evaluate the diagnostic criteria and imaging methods for bronchiectasis using CT and MRI.[19] The most used criterion for diagnosing bronchiectasis was an inner airway-artery ratio ≥ 1.0, used in 43% of the 122 reviewed studies. However, no validation studies for this cut-off value were found. Other criteria included the lack of tapering of the airways and the presence of airways visible within 1-3 cm of the pleura or the outer one-third of the lung. The review identified 42 different scoring methods used to quantify bronchiectasis, indicating a lack of standardization in the field. This again emphasized the strong lack of uniformity and the high need for standardized and, equally important, sufficiently validated imaging acquisition and analysis protocols to improve consistency in diagnosing and quantifying bronchiectasis, as well as standardized definitions and validated age-specific cut-off values.

The EMBARC Registry: Disease Quantification is a Must

In chapter 2, we used the BEST-CT manual scoring system to analyse CT scans from 524 bronchiectasis patients included in the European Bronchiectasis Registry (EMBARC) to investigate the nature and extent of structural lung abnormalities (SLA) and their relationship to clinical features, using subscores for different radiological features of bronchiectasis disease. Notably, inclusion into the registry is based on the presence of bronchiectasis per judgment of the investigator, but without any measure of the character or extent of the radiological abnormalities. The range of all types of structural abnormalities on the CT scans varied widely, from 0 tot 88%. Our findings revealed considerable heterogeneity in the type and extent of SLAs among patients. Mean subscores included total bronchiectasis (TBE) at 4.6%, total mucus plugging (TMP) at 4.2%, total inflammatory changes (TinF) at 8.3%, and total disease (DIS) at 14.9% of the ten scored predefined, evenly spaced axial CT slices . Patients with primary ciliary dyskinesia exhibited more extensive SLAs, while those with COPD had fewer SLAs. Lower FEV_1, longer disease duration, *Pseudomonas aeruginosa* and NTM infections, and severe exacerbations were all independently associated with more extensive SLAs.

These findings align with and expand on previous research. Reiff et al. demonstrated that CT imaging provides some ability to differentiate between specific causes

of bronchiectasis, such as central bronchiectasis in allergic bronchopulmonary aspergillosis or lower lobe predominance in mucociliary clearance disorders, though these distinctions are often insufficient for etiological differentiation in individual cases.[20] Similarly, Lynch et al. found weak but significant correlations between CT features, such as bronchiectasis extent and bronchial wall thickening, and spirometry values of FEV_1 and FVC, while noting that cystic bronchiectasis was associated with purulent sputum and *Pseudomonas* colonization.[21] Ooi et al. further demonstrated that bronchial wall thickening and small-airway abnormalities were linked to sputum volume and exacerbation frequency, with bronchial wall thickening emerging as a significant determinant of airflow obstruction after multivariate analysis.[15] These studies support the notion that a focus on specific abnormalities such as wall thickening and mucus plugging can be useful for patient differentiation.

The findings from our study build on these results by giving a more detailed quantification of structural abnormalities in a large and diverse bronchiectasis cohort, showing the significant heterogeneity in SLAs and their associations with patient characteristics and clinical outcomes., Our results suggest that quantitative CT analysis would be a valuable tool for clinicians to phenotype bronchiectasis patients and to potentially individualize treatment. Indeed, the notion that the presence of mucus plugging may identify patients that could benefit from mucolytic therapies has been supported by Dutch bronchiectasis guidelines.[6] Also, a recent post-hoc analysis from the BAT-trial has shown that azithromycin maintenance therapy led to an improvement of radiologic features including mucus impaction.[22] Future investigations should use structural abnormalities to select patients for treatment, as well as establish them as radiological endpoints of treatment effect. Achieving this goal would be greatly facilitated by efficient, objective and quantitative measurements.

The Telescope Effect: What Is It That We See?

The arrival of automated image analysis in radiology can be compared to the introduction of the James Webb telescope in astronomy.[23] Just as the telescope has provided incredibly detailed images of the universe with a whole new level of resolution, advanced imaging techniques give us detailed measurements of the various lung components that were previously not available. However, the first task, much like interpreting the vast data from a new telescope, is to make sense of what it actually is that we are seeing. A single CT scan can now generate a very large amount of data on airway dimensions, wall thickness, vascular dimensions, mucus plugs, and other abnormalities. Yet, while these automated tools appear to hold great promise to better inform us about a patient's condition, it remains uncertain which metrics will ultimately give the most

clinical value. This flood of new information requires careful analysis to cross-check the new, automatically generated data with established methods of analysis, such as manual CT scoring, spirometry and clinical judgment. Similarly, in Hans Castorp's case from the introductory citation, the optical results from the early X-ray image were checked for their correspondence with acoustic results, i.e. the tapping and auscultation findings from the physical examination, and found to correspond precisely.

Automated Imaging: Objective Quantification at Scale

Using the automated Bronchus-Artery (BA) method, we can detect and quantify a large number of bronchi and BA-pairs to obtain precise measurements of BA-dimensions on chest CT scans. These BA measures were first validated against manually annotated CT scans by Kuo et al.[24], finding good reliability in the assessment of bronchiectasis.[25, 26] In chapter 3 of this thesis, in a cohort of bronchiectasis patients participating in the iBEST clinical trial [27], we demonstrated that BA-dimensions for bronchial widening correlated with outcomes from the visual BEST-CT scoring method. Furthermore, airway wall thickness and wider bronchial lumen diameter assessed by the BA-method correlated with spirometry indices of airflow obstruction, such as FEV_1 and FEV_1/FVC. This study serves as an important validation of the BA-method, in particular showing that the higher cut-off values of BA-ratios for bronchiectasis and wall thickening correlate well with BEST-CT, and demonstrated the potential to provide clinicians with objective assessments of a large number of bronchi in the context of a clinical trial. This compliments other studies assessing the application of such automated measurements, for example Dournes et al. demonstrated the value of AI-derived radiologic markers to assess treatment effect in a cohort of CF patients using lumacaftor/ivacaftor.[28] Furthermore, Diaz et al. in an observational study of the large COPDGene cohort also showed their ability to quantify bronchiectasis using airway-to-artery ratios and the link to a higher total number of exacerbations.[29] Such studies have built a strong case that, using automated tools, information of high clinical relevance can be gathered from large sets of CT scans.

Thus, in Chapter 4, the BA-method was applied to the EMBARC bronchiectasis cohort, providing automated measurements of BA dimensions and mucus plug metrics to evaluate their relationships with visual BEST-CT findings and clinical characteristics. The analysis revealed significant correlations between automated BA measures, such as B_{out}/A and B_{wt}/A ratios, and clinical parameters, including spirometry indices like FEV_1, as well as bronchiectasis severity scores. Mucus plug counts and volumes also showed strong associations with disease activity markers, such as *Pseudomonas aeruginosa* infection and hospital admissions. These findings highlight the added value

of automated quantitative imaging for identifying phenotypic differences among bronchiectasis patients, showing the potential to improve patient stratification and disease monitoring. Moreover, the ability to detect mild bronchial dilatation and its potential application to monitor progression over time demonstrates the BA-method's utility in providing clinicians a more nuanced understanding of the pathological changes in their patients. Additionally, this study shows the feasibility of integrating automated imaging biomarkers into large patient registries like EMBARC, paving the way for broader clinical adoption and identification of phenotypes and high-risk subgroups for different treatment strategies. Importantly, the objective quantification of bronchial wall thickness is another less explored parameter which, as a surrogate of chronic inflammatory bronchial remodeling and wall adherent mucus plaques, can be used not only in the area of bronchiectasis but also in asthma, COPD and other subjects with chronic inflammation and frequent airway infections.

In chapter 5, the BASIIS study explored the relationship between automated radiological markers of both wall thickness and mucus plugs with clinical characteristics. The findings revealed a moderate to strong relationship between increased airway wall thickness and mucus plugs with reduced spirometry values, underscoring their role as drivers of airflow limitation. Additionally, these markers showed strong associations with bronchiectasis severity indices, which are predictive of mortality and hospitalization risk, as well as independent associations with the presence of *Pseudomonas aeruginosa* and frequent exacerbations.

The study also examined the influence of blood eosinophil counts in bronchiectasis patients with an asthma co-diagnosis. No significant relationship was found between blood eosinophil counts and radiological markers, suggesting that either blood eosinophils are an imperfect marker or that eosinophilic inflammation may not play an important role in the investigated bronchiectasis cohort, even though the participants had coexisting asthma. These findings align with the EMBARC bronchiectasis cohort in Chapter 4, where elevated eosinophil counts showed no significant correlation with BA measures or mucus plugs, although a subgroup analysis for coexisting asthma is planned.

These findings appear to contrast with those of Inoue et al., who demonstrated a positive correlation between induced sputum eosinophil differential counts and CT-assessed airway wall thickness in eosinophilic asthma patients, indicating a difference in patient category or that localized eosinophilic activity may be more closely related to airway remodeling than systemic measures like blood eosinophils.[30] Additionally, Bendien et al. reported significantly higher mean blood eosinophil counts in severe asthma patients with bronchiectasis compared to those without bronchiectasis (0.80

vs. 0.40), suggesting that the presence of bronchiectasis in severe asthma could reflect an overlap phenotype with greater eosinophilic activity.[31] Together, these studies highlight the complexity of the relationship between eosinophilic inflammation and radiological abnormalities in airway diseases.

The relevance of mucus plugs was further assessed in chapter 6 in the large COPDGene cohort, which allowed us to quantify mucus plugs and their relationship with the ultimate clinical outcome, death, in COPD patients. Importantly, this study found almost exactly the same result as a previous manual mucus plug counting study by Diaz et al., underscoring the reproducibility and validity of the findings.[18] Possibly, many of the mucus plugs identified in these studies are symptomatically silent, as also highlighted in a previous study by Dunican et al.[32] Their study demonstrated that 57% of 400 smokers with COPD had mucus plugs on CT scans, yet only a minority reported mucus-related symptoms. This finding underscores the potential for silent plugs to contribute to disease progression without clear clinical symptoms, supporting imaging-based detection strategies. In their study, mucus plugs were also associated with airflow limitation, exacerbations and hypoxemia. Thus, the associations between mucus plug burden and negative outcomes, including all-cause mortality, shows the role of mucus as a biomarker and risk predictor. Measuring mucus plugs can help monitor disease progression and stratify risk, particularly in patients who may not have obvious symptoms. However, moving beyond our 'simple' analysis on mortality of chapter 6, more investigations are needed to understand the interactions of mucus with patient characteristics such as systemic inflammation, pathogens (e.g. *Pseudomonas*) airflow limitation and emphysema. Additionally, assessing mucus volume and lobar distribution is essential to potentially define mucus-dominant phenotypes and evaluate the effectiveness of mucus clearing therapies. Importantly, the exact causal pathway linking mucus and mortality remains unclear. While mucus reduction strategies appear promising, it is possibly too simplistic to assume that simply reducing mucus would also reduce mortality without addressing the underlying pathological mechanisms.

In light of the results discussed above, it is evident that by not implementing these techniques, a huge resource of highly relevant information on our patients would be left unused. Manual scoring is simply not feasible due to the time-consuming nature of such analysis, but automated tools can bridge the gap from research to clinic.

From Research to Clinic: Validating AI for Airways

While the automated BA-method provides an assessment that is both efficient and objective, broader adoption, comparable to the use of FEV_1 in clinical practice, will

require more validation and population studies. Such studies should aim to establish cut-off values, for both bronchial and arterial dimensions as well as their ratios, to distinguish normal from pathological states. Also, different automated techniques will have different strengths and drawbacks, such as for example the influence of pathophysiological changes in the arterial dimensions on BA-ratios has until now been insufficiently investigated. Recent analyses by our group have supported the concept that COPD is equally a vascular disease with important changes to the vasculature in more severe disease stages, potentially making a bronchial ratio relative to the artery a moving target.[33, 34] Indeed, in the BASIIS study (Chapter 5), it was shown that B_{wa}/B_{oa} and Pi10 as measures of wall thickness that are independent of arterial dimension provided insights into structural changes without the potentially confounding influence of altered arterial size. The results demonstrated that these measures were also correlated with spirometry and other clinical factors, underscoring their use in measuring airway remodeling and its functional effect.

Other important steps will be the development of standardized CT protocols. Standardization of scan settings, such as KV, mA, slice thickness, and reconstruction kernels, is critical to reduce variability across centers and improve data quality. Variability in technical parameters and inspiratory and expiratory levels significantly impacts the interpretation of CT scans. Efforts by the Radiological Society of North America (RSNA) through the Quantitative Imaging Biomarkers Alliance (QIBA) have provided valuable resources for addressing this challenge.[35] The QIBA protocols for different scanner manufacturers, although developed with a focus on COPD, serve as a good example of how standardization efforts could drive uniformity and reproducibility in imaging. Applying a similar approach to the study of bronchiectasis could greatly enhance the use of imaging biomarkers in this area.

Another possibility is CT timing using spirometry to ensure consistent and accurate lung volumes during scanning.[31, 32] This may improve the reliability of quantitative assessments, minimizing variability due to differences in inspiration levels, particularly in pediatric patients.[36] Furthermore, advancements in CT technology may further enhance resolution, allowing for the capture of a greater number of airways. Given that using current standard CT scans the algorithms only capture on average around 200 bronchial-arterial (BA) pairs out of the theoretically over 1100 bronchi (dichotomous branching) in segmental bronchi generations 1-6, efforts should be directed towards optimising lung volume for chest CTs, increasing the resolution and sensitivity of CT imaging to provide a more comprehensive representation.[37]

Another key improvement involves incorporating expiratory scans into protocols to assess air trapping, diaphragm movement, and airway collapse. Expiratory scans,

though challenging due to inter-operator variability and patient cooperation, offer additional insights into airway diseases. Low-dose protocols for expiratory imaging may enable this without significant increases in radiation exposure.[38, 39]

Finally, obtaining large datasets for training, validation, and the establishment of reference values for non-diseased individuals will be critical. Efforts like the Normal Chest CT Study Group can provide essential reference data.[40] In this regard, it is unfortunate that the author's attempt to apply BA-analysis to the CT scans from the ERGO cohort were hindered by technical limitations. Hopefully, future technical solutions and newer scan protocols will solve this obstacle and provide us with population reference values of these airway measures.

Advancing Disease Monitoring: PRM and Beyond

Looking beyond the here investigated AI-assisted quantitative techniques, newer AI technologies for CT image analysis may present further opportunities to advance the understanding and clinical management of bronchiectasis and other respiratory diseases.

One promising area is the use of saliency mapping, which can highlight the most relevant features in CT scans for disease assessment. When using single or combined AI-derived parameters for prediction of clinical outcomes or response to therapy, saliency mapping can visualize which parts of the CT image are driving a model's predictions. This technique can identify subtle radiological features with the strongest relationships to outcomes of interest, which may not always align with traditional interpretations or might have been previously overlooked. Although current deep learning saliency map applications have not yet performed well enough for clinical application, developments in this area are moving fast. [41]

Another innovative approach is progression mapping, which involves the longitudinal analysis of multiple CT scans to track disease progression over time. By automatically comparing sequential scans, AI can detect small changes in airway dimensions such as wall thickness and mucus plugs, providing the clinician with regions of interest. Integrating multiple scans into 'movie clips' of changes over time enables an improved dynamic understanding of disease evolution, offering insight into a patient's trajectory, with possible cues for intervention.[42]

Parametric response mapping (PRM) is another advanced imaging approach that has shown promise in quantifying functional and structural changes over time. Originally

developed to assess lung parenchymal changes in diseases like COPD, PRM overlays paired inspiratory and expiratory CT scans to visualize regional variations in ventilation and air trapping, even down to the level of individual bronchial segments The technique distinguishes healthy lung areas from regions affected by small airway disease or emphysema.[43] Applying PRM to bronchiectasis could add insight into dynamic airway function. By combining PRM with assessments of airway wall thickness, bronchial dilation, and mucus plugging, researchers could gain a more complete view of disease mechanisms and their functional consequences.

These developments can transform CT image analysis from a static, subjective practice into a dynamic, objective tool. By providing actionable insights into disease progression, treatment response, and phenotype-specific management, these technologies promise to greatly enhance both our understanding and patient care. . The ultimate validation of these approaches will depend on their integration into a continuous cycle of measuring, treating, re-measuring, and evaluating outcomes to ensure that the insights lead to clinical benefits. To enable this cycle, it is critical that automated tools become integrated in existing PACS systems and readily available to clinicians at point-of-care.

Impact of Anti-inflammatory Therapies

Chronic airway inflammation plays a central role in the pathophysiology of bronchiectasis, asthma and COPD, and has been correlated with symptoms of cough, sputum production, dyspnea, and frequent exacerbations.[44] Among the inflammatory mechanisms involved, eosinophilic inflammation, a prototype of type 2 (T2) immune responses, stands out as a significant but complex phenomenon in chronic airway diseases. Eosinophils contribute to airway inflammation through their role in promoting mucus production, inflammation, and contributing to tissue damage, which makes them a central focus for therapeutic strategies in asthma.[45]

In asthma, where T2 inflammation dominates, eosinophil counts are a reliable biomarker to guide treatment decisions, particularly for the use of ICS and biologics targeting the IL-4, IL-5, or IL-13 pathways. Beyond asthma, however, the role of eosinophilic inflammation in bronchiectasis and COPD remains less clear. While a subgroup of bronchiectasis patients exhibits eosinophilic inflammation, others are predominantly driven by neutrophilic or mixed inflammatory mechanisms, complicating the selection of appropriate therapies.[44, 46] In addition, the instability of blood eosinophil levels in bronchiectasis further challenges their utility as reliable biomarkers for T2 inflammation or corticosteroid efficacy.[47]

In this thesis, the role of eosinophilic inflammation in bronchiectasis was a relevant consideration in the analysis of the CT scans of a cohort of patients with bronchiectasis and asthma, as well as evaluations of ICS/LABA combination therapy and biologic agents (chapter 5, chapter 7 and chapter 8, respectively). Understanding the contribution of eosinophils in bronchiectasis could enable clinicians to better stratify patients for therapies that specifically target T2 inflammation, potentially reducing disease burden and improving clinical outcomes.

ICS/LABA in Bronchiectasis: Lessons from FORZA

Inhaled corticosteroids (ICS), often in combination with long-acting beta-agonists (LABA) are the cornerstone of asthma treatment.[48] ICS work by reducing (T2) inflammation, in particular eosinophilic inflammation, within the airways, decreasing the frequency and severity of asthma symptoms and exacerbations. LABA, on the other hand, help in relaxing the smooth muscles around the airways, providing sustained bronchodilation. The combination of ICS and LABA (ICS/LABA) has been shown to improve lung function, control symptoms, and enhance the quality of life in asthma patients.[48]

Beyond asthma, the application of ICS/LABA has been explored in other chronic respiratory diseases, notably chronic obstructive pulmonary disease (COPD) and bronchiectasis. In COPD, ICS/LABA combination therapy is used to manage symptoms and prevent exacerbations, and has been included in the guidelines for selected COPD patients with frequent exacerbations (≥2/year), hospitalizations, an eosinophilic endotype (≥300 cells/μL) or concomitant asthma.[49] However, while studies demonstrated that ICS/LABA can reduce exacerbation frequency, they may also increase the risk of pneumonia in COPD patients. The benefit of ICS/LABA in bronchiectasis is doubtful.

In chapter 7 of this thesis, the FORZA study evaluated the efficacy of combined beclomethasone-formoterol inhalation in reducing chronic cough in bronchiectasis patients without asthma or COPD. The rationale for the study was primarily that older studies had showed some benefits of ICS/LABA or ICS alone, but did not include a placebo control group, nor excluded asthma or COPD.[50-54]

Despite the early termination of the study due slow accrual and the COVID-19 pandemic, the results indicated no significant differences in cough scores, lung function, or quality of life between the treatment and placebo groups. The increased incidence of adverse events in the treatment group suggested that caution is warranted when

prescribing ICS/LABA for bronchiectasis patients without asthma or COPD. These findings highlight the issues with undifferentiated prescription of anti-inflammatory therapies and suggest the need for better patient selection. Indeed, subsequent cohort analyses have suggested that ICS prescription has a beneficial effect on exacerbations in the subcategory of patients with peripheral blood eosinophils ≥3%.[55, 56] However, recent studies have indicated that blood eosinophil counts may actually be variable in bronchiectasis.[47] Also, blood eosinophils in bronchiectasis may, like in COPD, not reliably discriminate for T2 inflammation and corticosteroid efficacy, as multiple inflammatory pathways are involved.[57] Unfortunately, the FORZA study was underpowered to do a post-hoc subgroup analysis based on blood eosinophil counts, so unable to confirm the mentioned cohort studies.

Biologics for Airway Diseases

Biological therapies, which are monoclonal antibodies that target specific intermediaries in the inflammatory process, have transformed the management of severe asthma. Agents such as omalizumab, mepolizumab, benralizumab, dupilumab and tezepelumab target different mediators in the T2 immune response, leading to reduced exacerbations, improved lung function, and enhanced quality of life in patients with severe asthma. These biologicals are currently investigated for their potential use in other respiratory conditions, including COPD and bronchiectasis, given their success in modulating complex immune pathways in asthma. However, targeting the right patient with the right biological has proven to be difficult. In COPD, some studies investigating mepolizumab or benralizumab in patients with high eosinophil levels turned out negative, most importantly for the number of exacerbations.[58-60] However, dupilumab has recently shown efficacy in reducing exacerbations and mucus plugs in COPD, suggesting potential for bronchiectasis patients with similar T2 inflammatory endotypes.[61] In bronchiectasis, no biological trials have been conducted, but case series have indicated the efficacy of anti-IL-5.[62] Promising results have been described for both benralizumab and dupilumab on the reduction of mucus plugs in asthma patients, which again may also be relevant for mucus-obstructed bronchiectasis patients with an underlying T2 pathophysiology.[63, 64] Additionally, a therapy like tezepelumab, which acts higher in the inflammatory cascade, may address both T2 and IL-17-driven neutrophilic inflammation, so with a broader anti-inflammatory mode of action.[65, 66]

In this thesis, dupilumab in an ABPA case series demonstrated the potential of biologic agents in modulating the T2 immune response and improving clinical outcomes. ABPA is characterized by a hypersensitive response to *Aspergillus fumigatus,* leading to excessive

inflammation, bronchial damage, and mucus plugging. Conventional treatments for ABPA typically involve corticosteroids and antifungal agents, which, although effective, can have serious adverse effects, including immunosuppression and toxicity.

Dupilumab, a monoclonal antibody targeting the IL-4 receptor alpha subunit, blocks both IL-4 and IL-13 signaling pathways. This dual blockade reduces IgE production, eosinophil recruitment to tissues, and overall T2-driven inflammation.[67] In our case series, treatment led to significant improvements in symptoms, exacerbation rates, lung function, and reductions in prednisone use and IgE levels. Although a case series is an uncontrolled study, these findings suggest that dupilumab offers an effective alternative for managing ABPA, providing a new line of treatment next to the conventional ABPA therapies. A Phase 2 trial investigating dupilumab specifically for ABPA is currently still underway.[68] However, a recommendation to use dupilumab has recently made it to the most recent ABPA guidelines, although with a low level of evidence and low level of consensus, reflecting differing opinions among experts.[69]

Future directions in the management of bronchiectasis with anti-inflammatory therapies involve the continued exploration of biological agents. Given the success of dupilumab in ABPA and other reports, there is much room for other biologics to be tested in bronchiectasis. Investigating the efficacy and safety of biologics like mepolizumab and benralizumab, which target eosinophilic inflammation through IL-5, could be of benefit in eosinophilic bronchiectasis. However, patient selection remains challenging. Since blood eosinophil levels may be less stable or reflective of T2 inflammation in bronchiectasis patients than in asthma, sputum eosinophils could be a better indicator of active eosinophilic airway inflammation, which in the future can potentially be measured by point-of-care assays.[70]

Neutrophils and Mucus Plugs

Anti-neutrophilic approaches present a new direction in anti-inflammatory treatment for bronchiectasis and other airway diseases. Neutrophil elastase, an enzyme released during neutrophil activation, is closely linked to bronchiectasis severity and disease progression. It contributes to tissue damage, mucus hypersecretion, and exacerbations. [5, 44] Neutrophils form neutrophil extracellular traps (NETs), which are web-like structures composed of DNA, histones, and granular proteins such as myeloperoxidase (MPO) and neutrophil elastase. Interestingly sputum colour, reflecting the level of neutrophilic inflammation through MPO, was shown to be an objective predictor of exacerbation risk.[71, 72] NETs, designed to trap pathogens, paradoxically worsen airway inflammation by increasing mucus viscosity and elasticity and inducing pro-

inflammatory cytokines such as IL-8 and IL-6 from airway epithelial cells. NETosis, the process of NET formation has been implicated in both the development and exacerbation of airway diseases, including asthma and COPD.[73] Moreover, high levels of extracellular DNA (eDNA), originating from NETosis, have been associated with poorer outcomes and more severe airway obstruction.

Azithromycin (AZM), a macrolide antibiotic, has become a cornerstone of management of bronchiectasis, with robust evidence demonstrating its efficacy in reducing exacerbation frequency.[74, 75] Beyond its antimicrobial properties, AZM exerts immunomodulatory effects, particularly by reducing IL-8 and other pro-inflammatory cytokines.[76] Its long-term use has also been shown to improve radiologic features, as evidenced by a recent post-hoc analysis from the BAT trial, where maintenance AZM therapy led to reductions in mucus impaction and other radiologic markers of bronchiectasis on CT scans.[22] These findings affirm AZM as an essential component of therapeutic strategies targeting neutrophilic inflammation in bronchiectasis. [6, 7] Additionally, AZM has shown efficacy in reducing exacerbations in selected patients with COPD and asthma.[48, 49]

Treatments targeting eDNA, such as dornase alfa, have shown great efficacy in cystic fibrosis, but not in (non-CF) bronchiectasis, asthma, and COPD.[77] However, perhaps it may be effective in carefully selected patients with high neutrophilia or high numbers of exacerbations. Studies have revealed links between neutrophilic inflammation and the severity of radiological abnormalities in patients with bronchiectasis as well as asthma and COPD patients, again underscoring the potential to use CT features for patient selection. [78-80]

Recent trials with the neutrophil elastase inhibitor brensocatib have shown promise, demonstrating reduced exacerbations.[81, 82] By inhibiting neutrophil elastase, brensocatib addresses the key pathogenic factor in bronchiectasis, potentially offering a targeted treatment strategy that complements existing therapies. In fact, the development of brensocatib is the first drug specifically developed in the long-neglected field of bronchiectasis and is eagerly awaited by patients and physicians. Interestingly, targeting neutrophilic inflammation via neutrophil elastase inhibitors may also be effective in selected COPD subgroups and should gain renewed interest from investigators and pharmaceutical companies.[83, 84] Perhaps neutrophil elastase activity can also be measured using point-of-care sputum assays for patient selection and response monitoring.[85] But again, subgroups of patients that are likely to respond to this therapy may also be identified through filtering specific radiological features with the help of AI tools. In this regard, the results of the LungQ analysis of the CT scans

of the phase III brensocatib trial (as carried out by LungAnalysis) will be extremely interesting.

Tezepelumab, already mentioned before for its ability to modulate upstream inflammatory pathways, may also hold promise in addressing neutrophilic inflammation. By targeting thymic stromal lymphopoietin (TSLP), tezepelumab can reduce IL-17A and IL-8 activity, which, as discussed, are key drivers of neutrophil recruitment and activation.[66] This dual anti-eosinophilic and anti-neutrophilic mechanism makes it a compelling candidate for treating airway diseases characterized by mixed or shifting inflammatory endotypes. Interestingly, a positive effect of tezepelumab on mucus plugs has already been demonstrated in moderate-to-severe asthmatics. [86] Even more aggressive management strategies may combine such drugs, with for example brensocatib's inhibition of neutrophil elastase could complement tezepelumab's upstream modulation of neutrophil recruitment, providing a double approach to controlling neutrophilic inflammation.

In conclusion, while traditional inhalator therapies like ICS/LABA have shown limited benefit when prescribed in unselected bronchiectasis disease patients, the establishment of an eosinophil-driven subgroup as well as the emergence of biologicals and novel anti-neutrophilic treatments offers new hope. Ideally, a precision medicine approach could select the right patients through inflammatory endotyping as well as using radiologic markers of inflammation such as wall thickness and mucus plugs to optimize treatment approach.

Concluding Remarks

Reflecting on Thomas Mann's description of the revealing nature of early X-ray diagnostics, this thesis was built onto the advancements and persistent challenges in understanding and managing bronchiectasis disease, asthma, and COPD. Just as the invisible destruction caused by tuberculosis was brought to light, the studies in this thesis have demonstrated how modern high-resolution computed tomography and automated quantitative image analysis reveal new, complex and until now hidden abnormalities within the lungs of patients with these chronic airways diseases. The two studies in this thesis on anti-inflammatory therapies highlight the need for personalized medicine, showing both the potential of targeted biologicals therapy as well as the risk of increased adverse events when an intervention is not matched to the underlying pathophysiological mechanism. Fortunately, inflammatory endotyping will likely be a dominant paradigm for future studies on the expanding arsenal of anti-inflammatory therapies.

Moving ahead from this thesis, radiological and inflammatory markers must become integrated in a unified strategy for managing these complex diseases. However, the impact of these advancements depends on bringing them into routine clinical practice, particularly through clinical implementation of automated imaging metrics as well as reliable, point-of-care inflammatory markers and a growing arsenal of targeted anti-inflammatory treatments. This will empower clinicians with information and options for each patient's unique disease profile. By combining all the available data we can develop more effective, personalized treatments, delivered at the right time to those patients most at risk. With continued research and innovation, we can look forward to a future where patients with these chronic airway diseases experience significantly improved health and quality of life.

References

1. Naidich, D.P., et al., *Computed tomography of bronchiectasis.* J Comput Assist Tomogr, 1982. **6**(3): p. 437-44.
2. Austin, J.H., et al., *Glossary of terms for CT of the lungs: recommendations of the Nomenclature Committee of the Fleischner Society.* Radiology, 1996. **200**(2): p. 327-31.
3. Brightling, C. and N. Greening, *Airway inflammation in COPD: progress to precision medicine.* Eur Respir J, 2019. **54**(2).
4. Svenningsen, S. and P. Nair, *Asthma Endotypes and an Overview of Targeted Therapy for Asthma.* Front Med (Lausanne), 2017. **4**: p. 158.
5. Martins, M., H.R. Keir, and J.D. Chalmers, *Endotypes in bronchiectasis: moving towards precision medicine. A narrative review.* Pulmonology, 2023. **29**(6): p. 505-517.
6. Werf, T.v.d.e.a. *NVALT richtlijn Bronchiëctasieën*. 2017 06-19-2017 [cited 2024 05-27-2024]; Available from: https://richtlijnendatabase.nl/richtlijn/bronchiectasieen/startpagina_bronchiectasieen.html.
7. Polverino, E., et al., *European Respiratory Society guidelines for the management of adult bronchiectasis.* Eur Respir J, 2017. **50**(3).
8. Minov, J., et al., *Assessment of the Non-Cystic Fibrosis Bronchiectasis Severity: The FACED Score vs the Bronchiectasis Severity Index.* Open Respir Med J, 2015. **9**: p. 46-51.
9. Odry, B.L., et al., *Automated CT scoring of airway diseases: preliminary results.* Acad Radiol, 2010. **17**(9): p. 1136-45.
10. Weber, K., et al., *Cystic fibrosis in adults: short-term and long-term reproducibility of the Brody score for lung morphology in low-dose MDCT scans.* Rofo, 2014. **186**(1): p. 54-60.
11. Mandal, P., D. Patel, and A. Hill, *A simplified CT scoring system in non cystic fibrosis bronchiectasis.* European Respiratory Journal, 2013. **42**(Suppl 57): p. P241.
12. Rosenow, T., et al., *PRAGMA-CF. A Quantitative Structural Lung Disease Computed Tomography Outcome in Young Children with Cystic Fibrosis.* Am J Respir Crit Care Med, 2015. **191**(10): p. 1158-65.
13. Meerburg, J.J., et al., *Analysis of Granulomatous Lymphocytic Interstitial Lung Disease Using Two Scoring Systems for Computed Tomography Scans-A Retrospective Cohort Study.* Front Immunol, 2020. **11**: p. 589148.
14. Kosciuch, J., et al., *Relationship between airway wall thickness assessed by high-resolution computed tomography and lung function in patients with asthma and chronic obstructive pulmonary disease.* J Physiol Pharmacol, 2009. **60 Suppl 5**: p. 71-6.
15. Ooi, G.C., et al., *High-resolution CT quantification of bronchiectasis: clinical and functional correlation.* Radiology, 2002. **225**(3): p. 663-72.
16. Sheehan, R.E., et al., *A comparison of serial computed tomography and functional change in bronchiectasis.* Eur Respir J, 2002. **20**(3): p. 581-7.
17. Dunican, E.M., et al., *Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction.* J Clin Invest, 2018. **128**(3): p. 997-1009.
18. Diaz, A.A., et al., *Airway-Occluding Mucus Plugs and Mortality in Patients With Chronic Obstructive Pulmonary Disease.* JAMA, 2023. **329**(21): p. 1832-1839.
19. Meerburg, J.J., et al., *Diagnosis and quantification of bronchiectasis using computed tomography or magnetic resonance imaging: A systematic review.* Respir Med, 2020. **170**: p. 105954.
20. Reiff, D.B., et al., *Ct Findings in Bronchiectasis - Limited Value in Distinguishing between Idiopathic and Specific Types.* American Journal of Roentgenology, 1995. **165**(2): p. 261-267.

21. Lynch, D.A., et al., *Correlation of CT findings with clinical evaluations in 261 patients with symptomatic bronchiectasis.* American Journal of Roentgenology, 1999. **173**(1): p. 53-58.
22. Terpstra, L.C., et al., *The effect of maintenance azithromycin on radiological features in patients with bronchiectasis - Analysis from the BAT randomized controlled trial.* Respir Med, 2022. **192**: p. 106718.
23. Contributors, W. *James Webb Space Telescope*. 2024 June 26, 2024 July 1, 2024]; Available from: https://en.wikipedia.org/w/index.php?title=James_Webb_Space_Telescope&oldid=1231131730.
24. Kuo, W., et al., *Objective airway artery dimensions compared to CT scoring methods assessing structural cystic fibrosis lung disease.* J Cyst Fibros, 2017. **16**(1): p. 116-123.
25. Kuo, W., et al., *Diagnosis of bronchiectasis and airway wall thickening in children with cystic fibrosis: Objective airway-artery quantification.* Eur Radiol, 2017. **27**(11): p. 4680-4689.
26. Perez-Rovira, A., et al., *Automatic airway-artery analysis on lung CT to quantify airway wall thickening and bronchiectasis.* Med Phys, 2016. **43**(10): p. 5736.
27. Loebinger, M.R., et al., *Efficacy and safety of TOBI Podhaler in Pseudomonas aeruginosa-infected bronchiectasis patients: iBEST study.* Eur Respir J, 2021. **57**(1).
28. Dournes, G., et al., *Artificial intelligence in computed tomography for quantifying lung changes in the era of CFTR modulators.* Eur Respir J, 2022. **59**(3).
29. Diaz, A.A., et al., *Artificial Intelligence-based CT Assessment of Bronchiectasis: The COPDGene Study.* Radiology, 2023. **307**(1): p. e221109.
30. Inoue, H., et al., *CT-assessed large airway involvement and lung function decline in eosinophilic asthma: The association between induced sputum eosinophil differential counts and airway remodeling.* J Asthma, 2016. **53**(9): p. 914-21.
31. Bendien, S.A., et al., *Bronchiectasis in Severe Asthma: Does It Make a Difference?* Respiration, 2020: p. 1-9.
32. Dunican, E., et al., *Mucus Plugs and Emphysema in the Pathophysiology of Airflow Obstruction and Hypoxemia in Smokers.* American journal of respiratory and critical care medicine, 2020.
33. Kwee, A.K.A.L., et al., *Higher pulmonary artery and vein volumes are associated with disease severity and mortality in smokers with and without COPD.* European Respiratory Journal, 2023. **62**(suppl 67): p. PA3997.
34. van der Veer, T., et al., *CT-quantified pulmonary artery volume associates independently with higher mortality in smokers with and without COPD.* European Respiratory Journal, 2023. **62**(suppl 67): p. PA2284.
35. QIBA. *Quantitative Imaging Biomarkers Alliance Wiki*. 2024 17 January 2024 [cited 2024 5 December 2024]; Available from: https://qibawiki.rsna.org/index.php/Main_Page.
36. Mott, L., et al., *Assessment of early bronchiectasis in young children with cystic fibrosis is dependent on lung volume.* Chest, 2013. **144 4**: p. 1193-1198.
37. JA, E., et al., *Fishman's Pulmonary Diseases and Disorders, 5th Edition*. 2015: McGraw-Hill Education.
38. Chen, Y.X., et al., *Effect of inspiratory lung volume on bronchial and arterial dimensions and ratios on chest computed tomography in patients with chronic obstructive pulmonary disease.* European Radiology, 2024.
39. Kuo, W., et al., *Monitoring cystic fibrosis lung disease by computed tomography. Radiation risk in perspective.* Am J Respir Crit Care Med, 2014. **189**(11): p. 1328-36.
40. Lv, Q., et al., *Normative values for lung, bronchial sizes and bronchus-artery ratios in non-contrast and contrast-enhanced chest CT scans: a study of 375 patients from infancy into young adulthood*. 2025 (Sumbitted).

41. Saporta, A., et al., *Benchmarking saliency methods for chest X-ray interpretation.* Nature Machine Intelligence, 2022. **4**(10): p. 867-878.
42. Hoppe, B.P.C., B.C. Stoel, and P.E. Postmus, *Natural Course of Cysts in Birt-Hogg-Dube Syndrome.* Am J Respir Crit Care Med, 2022. **205**(12): p. 1474-1475.
43. Pompe, E., et al., *Progression of Emphysema and Small Airways Disease in Cigarette Smokers.* Chronic Obstr Pulm Dis, 2021. **8**(2): p. 198-212.
44. Long, M.B., et al., *Rethinking bronchiectasis as an inflammatory disease.* Lancet Respir Med, 2024.
45. McBrien, C.N. and A. Menzies-Gow, *The Biology of Eosinophils and Their Role in Asthma.* Front Med (Lausanne), 2017. **4**: p. 93.
46. Shoemark, A., et al., *Characterization of Eosinophilic Bronchiectasis: A European Multicohort Study.* Am J Respir Crit Care Med, 2022. **205**(8): p. 894-902.
47. Martínez-García, M.A., et al., *Reliability of blood eosinophil count in steady-state bronchiectasis.* Pulmonology, 2024.
48. Venkatesan, P., *2023 GINA report for asthma.* Lancet Respir Med, 2023. **11**(7): p. 589.
49. Agusti, A., et al., *Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD Executive Summary.* Am J Respir Crit Care Med, 2023. **207**(7): p. 819-837.
50. Martínez-García, M., et al., *Clinical efficacy and safety of budesonide-formoterol in non-cystic fibrosis bronchiectasis.* Chest, 2012. **141**(2): p. 461-468.
51. Martínez-García, M.A., et al., *Inhaled steroids improve quality of life in patients with steady-state bronchiectasis.* Respir Med, 2006. **100**(9): p. 1623-32.
52. Tsang, K.W., et al., *Inhaled fluticasone reduces sputum inflammatory indices in severe bronchiectasis.* Am J Respir Crit Care Med, 1998. **158**(3): p. 723-7.
53. Tsang, K.W., et al., *Inhaled fluticasone in bronchiectasis: a 12 month study.* Thorax, 2005. **60**(3): p. 239-43.
54. Wei, P., et al., *Combined inhaled corticosteroid and long-acting β2-adrenergic agonist therapy for noncystic fibrosis bronchiectasis with airflow limitation: An observational study.* Medicine (Baltimore), 2016. **95**(42): p. e5116.
55. Martinez-Garcia, M.A., et al., *Role of inhaled corticosteroids in reducing exacerbations in bronchiectasis patients with blood eosinophilia pooled post-hoc analysis of 2 randomized clinical trials.* Respir Med, 2020. **172**: p. 106127.
56. Martínez-García, M., et al., *The U-Shaped Relationship Between Eosinophil Count and Bronchiectasis Severity: The Effect of Inhaled Corticosteroids.* Chest, 2023. **164**(3): p. 606-613.
57. Pignatti, P., et al., *Do blood eosinophils strictly reflect airway inflammation in COPD? Comparison with asthmatic patients.* Respir Res, 2019. **20**(1): p. 145.
58. Dasgupta, A., et al., *A pilot randomised clinical trial of mepolizumab in COPD with eosinophilic bronchitis.* Eur Respir J, 2017. **49**(3).
59. Pavord, I.D., et al., *Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease.* N Engl J Med, 2017. **377**(17): p. 1613-1629.
60. Criner, G.J., et al., *Benralizumab for the Prevention of COPD Exacerbations.* N Engl J Med, 2019. **381**(11): p. 1023-1034.
61. Bhatt, S.P., et al., *Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts.* N Engl J Med, 2023. **389**(3): p. 205-214.
62. Oriano, M., et al., *T2-High Endotype and Response to Biological Treatments in Patients with Bronchiectasis.* Biomedicines, 2021. **9**(7).
63. Sakai, N., et al., *Effect of Benralizumab on Mucus Plugs in Severe Eosinophilic Asthma.* Int Arch Allergy Immunol, 2023. **184**(8): p. 783-791.

64. Anai, M., et al., *Successful treatment with dupilumab for mucus plugs in severe asthma.* Respirol Case Rep, 2023. **11**(1): p. e01074.
65. Menzies-Gow, A., et al., *Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma.* N Engl J Med, 2021. **384**(19): p. 1800-1809.
66. Diver, S., et al., *Effect of tezepelumab on airway inflammatory cells, remodelling, and hyperresponsiveness in patients with moderate-to-severe uncontrolled asthma (CASCADE): a double-blind, randomised, placebo-controlled, phase 2 trial.* Lancet Respiratory Medicine, 2021. **9**(11): p. 1299-1312.
67. Harb, H. and T.A. Chatila, *Mechanisms of Dupilumab.* Clin Exp Allergy, 2020. **50**(1): p. 5-14.
68. Clinicaltrials.gov. *Investigating Treatment With Dupilumab in Patients With Allergic Bronchopulmonary Aspergillosis (ABPA) (LIBERTY ABPA AIRED)*. 2020 2024-03-04 [cited 2024 July 1]; Available from: https://clinicaltrials.gov/study/NCT04442269.
69. Agarwal, R., et al., *Revised ISHAM-ABPA working group clinical practice guidelines for diagnosing, classifying and treating allergic bronchopulmonary aspergillosis/mycoses.* Eur Respir J, 2024. **63**(4).
70. Ali, M.M., et al., *A Rapid Sputum-based Lateral Flow Assay for Airway Eosinophilia using an RNA-cleaving DNAzyme Selected for Eosinophil Peroxidase.* Angew Chem Int Ed Engl, 2023. **62**(38): p. e202307451.
71. Murray, M.P., et al., *Sputum colour: a useful clinical tool in non-cystic fibrosis bronchiectasis.* Eur Respir J, 2009. **34**(2): p. 361-4.
72. Aliberti, S., et al., *Objective sputum colour assessment and clinical outcomes in bronchiectasis: data from the European Bronchiectasis Registry (EMBARC).* Eur Respir J, 2024. **63**(4).
73. Porto, B.N. and R.T. Stein, *Neutrophil Extracellular Traps in Pulmonary Diseases: Too Much of a Good Thing?* Front Immunol, 2016. **7**: p. 311.
74. Altenburg, J., et al., *Effect of Azithromycin Maintenance Treatment on Infectious Exacerbations Among Patients With Non-Cystic Fibrosis Bronchiectasis The BAT Randomized Controlled Trial.* Jama-Journal of the American Medical Association, 2013. **309**(12): p. 1251-1259.
75. Wong, C., et al., *Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial.* Lancet, 2012. **380**(9842): p. 660-667.
76. Parnham, M.J., et al., *Azithromycin: Mechanisms of action and their relevance for clinical applications.* Pharmacology & Therapeutics, 2014. **143**(2): p. 225-245.
77. Tarrant, B.J., et al., *Mucoactive agents for chronic, non-cystic fibrosis lung disease: A systematic review and meta-analysis.* Respirology, 2017. **22**(6): p. 1084-1092.
78. Simpson, J.L., D.G. Milne, and P.G. Gibson, *Neutrophilic asthma has different radiographic features to COPD and smokers.* Respir Med, 2009. **103**(6): p. 881-7.
79. Chalmers, J.D., et al., *Neutrophil Elastase Activity Is Associated with Exacerbations and Lung Function Decline in Bronchiectasis.* American Journal of Respiratory and Critical Care Medicine, 2017. **195**(10): p. 1384-1393.
80. Stanescu, D., et al., *Airways obstruction, chronic expectoration, and rapid decline of FEV(1) in smokers are associated with increased levels of sputum neutrophils.* Thorax, 1996. **51**(3): p. 267-271.
81. Information, I.I.M., *ASPEN Study: Phase 3 Study to Assess the Efficacy, Safety, and Tolerability of Brensocatib in Participants with Non-Cystic Fibrosis Bronchiectasis*. 2024.
82. Chalmers, J.D., et al., *Phase 2 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis.* N Engl J Med, 2020. **383**(22): p. 2127-2137.
83. Thulborn, S.J., et al., *Neutrophil elastase as a biomarker for bacterial infection in COPD.* Respir Res, 2019. **20**(1): p. 170.
84. Lucas, S.D., et al., *Targeting COPD: advances on low-molecular-weight inhibitors of human neutrophil elastase.* Med Res Rev, 2013. **33 Suppl 1**: p. E73-101.

85. Shoemark, A., et al., *A point-of-care neutrophil elastase activity assay identifies bronchiectasis severity, airway infection and risk of exacerbation.* Eur Respir J, 2019. **53**(6).
86. Nordenmark, L.H., et al., *Tezepelumab and Mucus Plugs in Patients with Moderate-to-Severe Asthma.* NEJM Evid, 2023. **2**(10): p. EVIDoa2300135.

Appendices

English Summary

Bronchiectasis is a complex chronic respiratory disease characterized by irreversible airway dilation, chronic inflammation, and mucus obstruction. This thesis investigates its clinical and radiological heterogeneity and underlying disease mechanisms, particularly in the context of overlapping conditions like asthma and COPD. By using advanced imaging techniques and evaluating the effect of anti-inflammatory therapies, it aims to improve disease phenotyping and support tailored treatment strategies.

In the general introduction in **Chapter 1**, the context of this thesis is established by discussing the rising prevalence and burden of bronchiectasis and its shared disease mechanisms with asthma and COPD. It explains the need for personalized therapeutic approaches and introduces advanced imaging techniques to better understand the disease. This sets the stage to explore the role of these tools for better disease management.

Building on this, **Chapter 2** examined the clinical implications of structural abnormalities in the European Multicenter Bronchiectasis Audit and Research Collaboration (EMBARC) BEST-CT study. By correlating visual CT scores with clinical outcomes in a large bronchiectasis cohort of 524 patients, it found that abnormalities such as mucus plugging, the extent of bronchial wall widening and bronchial wall thickening were associated with increased disease severity, higher exacerbation rates, worse lung function and *Pseudomonas aeruginosa* colonization. The study also showed the very high heterogeneity of bronchiectasis patients, showing a range from 0% to 88% abnormalities in the scored lung parenchyma, and demonstrated the value of CT scoring in distinguishing radiological phenotypes of bronchiectasis patients. This visual scoring approach provided a framework for further refining imaging analysis methods, which was the focus of the following chapters.

Chapter 3 introduced the automated bronchus-artery (BA) method, a technique that assesses the ratio of bronchial wall thickness to the accompanying pulmonary artery diameter. Using CT scans from 69 patients from the iBEST clinical trial, it demonstrated how automated metrics of bronchial widening (Bout/A≥1.5) were well correlated with visual scoring of bronchiectasis as well as FEV_1 and FEV_1/FVC, and showed that automated methods are better at detecting bronchial wall thickening. The study showed the potential of automated scoring to replace visual scoring for trials and clinical care. This set the stage for broader application of automation in larger datasets.

Thus, in **Chapter 4** the BA method was applied to a much larger dataset of CT scans of 609 patients from the EMBARC study, which quantified 135,489 bronchus-artery

pairs and detected over 12,000 mucus plugs. Bronchial dilatation and bronchial wall thickening were observed in 73% and 49% of all BA-pairs. As in the visual scoring study, increased wall thickness and mucus plugging was significantly associated with *Pseudomonas aeruginosa* infections, severe exacerbations and underlying primary ciliary dyskinesia. Patients with more extensive structural abnormalities had a higher risk of frequent (≥2) hospitalizations. Interestingly, patients with co-existing asthma and/or COPD diagnosis had less bronchial dilatation, but more bronchial wall thickening. This chapter not only validated the use of automated techniques in quantifying structural abnormalities but also links these findings to key clinical outcomes. The inclusion of patients with co-existing asthma or COPD highlighted the nuanced differences between these overlapping conditions.

Further focusing on asthma and COPD, in **Chapter 5**, we analyzed CT scans from 64 bronchiectasis patients with coexisting asthma. Automated measurements revealed that increased bronchial wall thickness and mucus plugs correlated negatively with lung function (FEV_1 and FEV_1/FVC) and positively with disease severity scores (BSI and FACED), as well as the no. of exacerbations and *Pseudomonas aeruginosa* colonization. Elevated blood eosinophil counts were not associated with imaging metrics, suggesting a limited role for eosinophilic inflammation in this cohort.

Expanding the discussion of mucus obstruction to COPD, **Chapter 6** evaluated its prognostic significance in COPD using the large COPDGene cohort of 9,399 COPD patients. Automated mucus plug quantification showed a significant association between mucus obstruction and increased all-cause mortality. Patients with three or more mucus-obstructed bronchial segments had a 27% higher mortality risk, highlighting mucus plugs as an important biomarker in COPD and a potential target for intervention. Interestingly, this automated assessment replicated the result of manual mucus plug counting investigations, but in a larger cohort and with increased efficiency.

In the second part of this thesis on therapeutic interventions, **Chapter 7** assessed anti-inflammatory therapy for bronchiectasis patients without asthma or COPD. The FORZA randomized controlled trial, enrolling 34 bronchiectasis patients without asthma or COPD, evaluated beclomethasone-formoterol inhalation therapy for the relief of chronic cough. Although the trial was terminated prematurely, the treatment did not improve cough-related quality of life and was found to be associated with more adverse events compared to the placebo group. These findings call for caution in prescribing ICS/LABA therapies for bronchiectasis patients without coexisting asthma or COPD, a practice which remains very widespread.

Finally, in **Chapter 8** targeted anti-inflammatory treatment was investigated in a case series of patients with allergic bronchopulmonary aspergillosis (ABPA) and asthma. As a prototypical Type-2 inflammation mediated type of bronchiectasis disease, there are strong mechanistic arguments to apply the biological dupilumab in ABPA. In this study, dupilumab reduced the need for treatment with steroids as well as the number of exacerbations, and improved lung function. These findings highlight the potential of targeted therapies in specific subgroups of bronchiectasis patients.

In the final discussion in **Chapter 9**, insights from the preceding chapters have been synthesized to discuss the great potential of automated imaging analyses and personalized treatment strategies in bronchiectasis care. Findings demonstrated that automated imaging metrics not only improve diagnostic precision but also provide critical prognostic information, connecting radiological metrics with functional and clinical outcomes. The investigation of anti-inflammatory therapies showed the importance of tailoring treatments to specific patient subgroups. The next essential step should be clinical implementation of these markers alongside further research on the integration of radiologic phenotypes and inflammatory endotypes for more targeted, patient-specific strategies. With continued research, innovation and translation into clinical practice, patients with chronic airway diseases may experience significantly improved health and quality of life.

Nederlandse Samenvatting

Bronchiëctasieën zijn een complexe chronische longaandoening die wordt gekenmerkt door irreversibele verwijding van de luchtwegen, chronische ontsteking en slijmophoping. Dit proefschrift onderzoekt de klinische en radiologische heterogeniteit van bronchiëctasieën, met name in de context van overlappende aandoeningen zoals astma en COPD. Door gebruik te maken van geavanceerde beeldvormingstechnieken en het evalueren van de effecten van anti-inflammatoire therapieën, heeft het als doel de fenotypering van de ziekte te verbeteren en gepersonaliseerde behandelingsstrategieën te faciliteren. In de algemene introductie in **Hoofdstuk 1** wordt de context van dit proefschrift geschetst door de toenemende prevalentie en ziektelast van bronchiëctasieën te bespreken, evenals de gedeelde ziektemechanismen met astma en COPD. De noodzaak van gepersonaliseerde therapeutische benaderingen wordt toegelicht, en geavanceerde beeldvormingstechnieken worden geïntroduceerd om de ziekte beter te begrijpen. Dit legt de basis voor het onderzoeken van de rol van deze tools in een betere ziektebehandeling.

In aansluiting hierop onderzocht **Hoofdstuk 2** de klinische implicaties van structurele afwijkingen in de Europese Multicenter Bronchiëctasie Audit en Research Collaboration (EMBARC) BEST-CT-studie. Door visuele CT-scores te correleren met klinische uitkomsten in een groot cohort van 524 patiënten met bronchiëctasieën, werd vastgesteld dat afwijkingen, zoals slijmpluggen, de mate van bronchiale verwijding en verdikking van de bronchiale wand werden geassocieerd met een verhoogde ernst van de ziekte, hogere frequentie van exacerbaties, slechtere longfunctie en kolonisatie met *Pseudomonas aeruginosa*. De studie toonde ook de grote heterogeniteit van bronchiëctasiepatiënten aan, met een variatie van 0% tot 88% afwijkingen in het gescoorde longparenchym, en benadrukte de waarde van CT-scoring bij het onderscheiden van radiologische fenotypes van patiënten met bronchiëctasieën. Deze visuele scoringsresultaten vormde een achtergrond voor verder onderzoek naar geautomatiseerde beeldanalysemethoden, wat het onderwerp was van de volgende hoofdstukken.

Hoofdstuk 3 introduceerde de geautomatiseerde bronchus-arterie (BA)-methode, een techniek die de verhouding beoordeelt tussen de dikte van de bronchiale wand en de diameter van de bijbehorende longslagader. Met behulp van CT-scans van 69 patiënten uit de iBEST klinische trial werd aangetoond hoe geautomatiseerde meting van bronchiale verwijding ($B_{out}/A \geq 1{,}5$) goed correleerde met visuele scoring van bronchiëctasieën, evenals met FEV_1 en FEV_1/FVC, en liet zien dat geautomatiseerde methoden beter waren in het detecteren van bronchiale wandverdikking. De studie toonde het potentieel van geautomatiseerde scoring aan om visuele scoring te vervangen

voor trials en kliniek. Dit vormde de basis voor bredere toepassing van automatisering in grotere datasets.

Zo werd in **Hoofdstuk 4** de BA-methode toegepast op een veel grotere dataset van CT-scans van 609 patiënten uit de EMBARC-studie, waarbij 135.489 bronchus-arterieparen werden gekwantificeerd en meer dan 12.000 slijmpluggen werden gedetecteerd. Bronchiale dilatatie en verdikking van de bronchiale wand werden waargenomen in respectievelijk 73% en 49% van alle BA-paren. Net als in de visuele scoringstudie waren een verhoogde wanddikte en slijmophoping significant geassocieerd met *Pseudomonas aeruginosa*-kolonisatie, ernstige exacerbaties en onderliggend primaire ciliaire dyskinesie. Patiënten met meer uitgebreide structurele afwijkingen hadden een hoger risico op frequente (≥2) ziekenhuisopnames. Interessant genoeg hadden patiënten met een co-existente diagnose van astma en/of COPD minder bronchiale dilatatie, maar meer verdikking van de bronchiale wand. Dit hoofdstuk valideerde niet alleen het gebruik van geautomatiseerde technieken voor het kwantificeren van structurele afwijkingen, maar koppelde deze bevindingen ook aan belangrijke klinische uitkomsten. De bevindingen in de subgroep van patiënten met co-existente astma of COPD benadrukte de nuanceverschillen tussen deze overlappende aandoeningen.

Vanaf **Hoofdstuk 5** werd verder gefocust op astma en COPD, met de analyse van CT-scans van 64 patiënten met bronchiëctasieën en co-existente astma. Geautomatiseerde metingen toonden aan dat een toegenomen dikte van de bronchiale wand en slijmophopingen negatief correleerden met de longfunctie (FEV_1 en FEV_1/FVC) en positief met scores van ziekte-ernst (BSI en FACED), evenals het aantal exacerbaties en *Pseudomonas aeruginosa*-kolonisatie. Verhoogde eosinofielen in het bloed waren niet geassocieerd met radiologische parameters, wat suggereert dat eosinofiele ontsteking een beperkte rol speelt bij de pathofysiologie van bronchiectasieen in deze groep.

In **Hoofdstuk 6** werd de prognostische betekenis van slijmpluggen in COPD onderzocht in de grote COPDGene-cohortstudie met 9.399 COPD-patiënten. Geautomatiseerde kwantificatie van slijmpluggen toonde een significante associatie aan tussen slijmpluggen en verhoogde mortaliteit door alle oorzaken. Patiënten met drie of meer door slijm geobstrueerde bronchussegmenten hadden een 27% hoger sterfterisico, wat slijmpluggen positioneert als een belangrijke biomarker in COPD en een potentieel doelwit voor interventie. Ook van belang is dat deze geautomatiseerde studie de resultaten van eens studie met visuele tellingen van slijmpluggen repliceerde, maar in een groter cohort en met verhoogde efficiëntie.

In het tweede deel van dit proefschrift, over therapeutische interventies, werd in **Hoofdstuk 7** anti-inflammatoire therapie voor patiënten met bronchiëctasieën zonder

astma of COPD belicht. De FORZA gerandomiseerde gecontroleerde studie, met 34 patiënten, onderzocht het effect van inhalatietherapie met beclometason-formoterol ter verlichting van chronische hoest. Hoewel de studie voortijdig werd beëindigd, verbeterde de behandeling de hoestgerelateerde kwaliteit van leven niet en ging de interventie gepaard met meer bijwerkingen vergeleken met de placebogroep. Deze bevindingen roepen op tot voorzichtigheid bij het voorschrijven van ICS/LABA-therapieën aan patiënten met bronchiëctasieën zonder co-diagnose van astma of COPD, een praktijk die echter nog steeds veel voorkomt.

In **Hoofdstuk 8** werd gerichte anti-inflammatoire behandeling onderzocht in een casusserie van patiënten met allergische bronchopulmonale aspergillose (ABPA) en astma. Als een vorm van bronchiëctasieën die bij uitstek wordt gemedieerd door Type-2 ontsteking zijn er sterke mechanistische argumenten voor het toepassen van biologische therapieën zoals dupilumab. In deze studie verminderde dupilumab de noodzaak van behandeling met steroïden, het aantal exacerbaties en verbeterde het de longfunctie. Deze bevindingen benadrukken het potentieel van gerichte anti-inflammatoire therapieën voor specifieke subgroepen van patiënten met bronchiëctasieën.

In de afsluitende discussie in **Hoofdstuk 9** werden inzichten uit de voorgaande hoofdstukken geïntegreerd om het grote potentieel van geautomatiseerde beeldanalyses en gepersonaliseerde strategieën in de behandeling van bronchiëctasieën te bespreken. De bevindingen in dit proefschrift toonden aan dat geautomatiseerde beeldvormingsparameters niet alleen de diagnostische precisie verbeteren, maar ook cruciale prognostische informatie bieden, waarmee ze de verbinding maken tussen radiologische parameters en functionele en klinische uitkomsten. Het onderzoek naar anti-inflammatoire therapieën benadrukte het belang van het afstemmen van behandelingen op specifieke patiëntsubgroepen. De volgende essentiële stap is de klinische implementatie van deze markers, samen met verder onderzoek naar de integratie van radiologische fenotypes en inflammatoire endotypes om gerichte, patiëntspecifieke strategieën te ontwikkelen. Met meer onderzoek, innovatie en implementatie in de klinische praktijk kunnen patiënten met chronische luchtwegziekten aanzienlijk verbeterde gezondheid en een hogere kwaliteit van leven ervaren.

PHD PORTFOLIO

Summary of PhD training and teaching
Name PhD student: T. (Tjeerd) van der Veer
Erasmus MC department: Pulmonary Medicine
Research School: Molecular Medicine
PhD period: 2020 - 2024
Promotor: Prof. Dr. J.G.J.V. Aerts / Prof. Dr. H.A.W.M. Tiddens
Co-promotor: Dr. G.J. Braunstahl

1. PhD training	Year	Workload (ECTS)
General academy skills and in-depth courses		
BROK course	2024	2.0
GCP course (2x)	2020, 2022	0.6
Research integrity course	2022	0.3
In-house training Castor EDC	2021	0.3
R introduction training (VIB)	2022	0.6
Advanced immunology (Erasmus MC)	2020	1.0
(Inter)national scientific presentations		
Dutch Lung Congress (DLC), poster presentation	2021	0.5
World Bronchiectasis NTM Congress (Prague), best poster award	2022	0.5
ERS Congress 2023 (Milan), poster presentations (2)	2023	1.0
Presentatie Regionale wetenschappelijke avond Hotel New York	2023	0.5
American Thoracic Society congress 2023, abstract and poster	2023	0.5
ERS Congress 2024 (Vienna), poster presentations (2)	2024	1.0
American Thoracic Society 2024 congress, abstract and poster	2024	0.5
(Inter)national scientific conferences and seminars		
ERS Virtual school cystic fibrosis	2022	1.0
European Conference Cystic Fibrosis Rotterdam (ECFS) (2 days)	2022	0.6
World Bronchiectasis NTM Conference (Prague) (3 days)	2022	0.9
ERS conference, digital due to Covid-19 pandemic (3 days)	2020	0.9
ERS conference, digital due to Covid-19 pandemic (3 days)	2021	0.9
ERS Congress 2023 (Milan) (3 days)	2023	0.9
ERS Congress 2024 (Vienna) (3 days)	2024	0.9
Advanced Bronchoscopy & EBUS course (Amsterdam) (3 days)	2023	0.9
SWAB/NVALT Dutch Guideline Committee Community Acquired Pneumonia (CAP)	2021-2023	2.0
Congres Pulmonale Infectieziekten	2023	0.3
Regionale refereeravond (3x/year)	2020-2023	3.6

Teaching activities		
Lecturer at Erasmus MC Medical School (Ba2) (2x)	2020	1.0
Lecturer at Erasmus MC Medical School (Ba2) (2x)	2021	1.0
Lecturer at Erasmus MC Medical School (Ba2) (2x)	2022	1.0
Lecturer at Erasmus MC Medical School (Ba2) (2x)	2023	1.0
Lecturer at Erasmus MC Technical Medicine (1x)	2023	0.5
Supervising students		
Supervising MSc final year medical student research project	2022	3.0
Supervising BSc 2nd year medical student honours project	2022	1.0
Total ECTS		30.7 / 30

List of publications

Tjeerd van der Veer; Eleni-Rosalina Andrinopoulou; Gert-Jan Braunstahl; Jean Paul Charbonnier; Victor Kim; Rudolfs Latisenko; et al. Association between automatic AI-based quantification of airway-occlusive mucus plugs and all-cause mortality in patients with COPD. *Thorax*. 2025-02. DOI: 10.1136/thorax-2024-221928.

Marijn Berg; Lisette Krabbendam; Esmee K. van der Ploeg; Menno van Nimwegen; Tjeerd van der Veer; Martin Banchero; et al. Evidence for altered immune-structural cell crosstalk in cystic fibrosis revealed by single cell transcriptomics. *Journal of Cystic Fibrosis*. 2025-02. DOI: 10.1016/j.jcf.2025.01.016.

Tjeerd van der Veer; Eleni-Rosalina Andrinopoulou; Punitkumar Makani; Gert-Jan Braunstahl; Harm A.W.M. Tiddens. Automated computed tomographic analysis of bronchial thickness and mucus plugs in bronchiectasis with asthma. *ERJ Open Research*. 2025-01-31. DOI: 10.1183/23120541.00736-2024.

Angelina L.P. Pieters; Qianting Lv; Jennifer J. Meerburg; Tjeerd van der Veer; Eleni-Rosalina Andrinopoulou; Pierluigi Ciet; et al. Automated method of bronchus and artery dimension measurement in an adult bronchiectasis population. *ERJ Open Research*. 2024-11. DOI: 10.1183/23120541.00231-2024.

Anastasia K.A.L. Kwee; Eleni-Rosalina Andrinopoulou; Tjeerd van der Veer; Leticia Gallardo-Estrella; Jean-Paul Charbonnier; Stephen M. Humphries; et al. Higher small pulmonary artery and vein volume on computed tomography is associated with mortality in current and former smokers. *eBioMedicine*. 2024-10. DOI: 10.1016/j.ebiom.2024.105366.

F.V. van Daalen; W.G. Boersma; E.M.W. van de Garde; F.M. van der Mooren; N. Roescher; J.A. Schouten; et al. Management of Community-Acquired Pneumonia in Adults: the 2024 Practice Guideline from The Dutch Working Party on Antibiotic Policy (SWAB) and Dutch Association of Chest Physicians (NVALT). SWAB: Stichting Werkgroep Antibioticabeleid. 2024-07-01

Angelina Pieters; Tjeerd van der Veer; Jennifer J. Meerburg; Eleni-Rosalina Andrinopoulou; Menno M. van der Eerden; Pierluigi Ciet; et al. Structural Lung Disease and Clinical Phenotype in Bronchiectasis Patients: The EMBARC CT Study. *American Journal of Respiratory and Critical Care Medicine*. 2024-07-01. DOI: 10.1164/rccm.202311-2109oc.

Tjeerd van der Veer; Johanna Margaretha de Koning Gans; Gerrit J. Braunstahl; Angelina L.P. Pieters; Johanna M.W. van den Berg; Rogier A.S. Hoek; et al. The effect of beclomethasone–formoterol versus placebo on chronic cough in patients with non-CF bronchiectasis: the FORZA randomised controlled trial. *European Respiratory Journal*. 2023-06. DOI: 10.1183/13993003.00186-2023.

Johnmary T. Arinze; Tjeerd van der Veer; Daniel Bos; Bruno Stricker; Katia M.C. Verhamme; Guy Brusselle. Epidemiology of unexplained chronic cough in adults: a population-based study. *ERJ Open Research*. 2023-05. DOI: 10.1183/23120541.00739-2022.

Tjeerd van der Veer; Marloes A. Dallinga; Johanna P.M. van der Valk; Jasper H. Kappen; Johannes C.C.M. in 't Veen; Menno M. van der Eerden; et al. Reduced exacerbation frequency and prednisone dose in patients with ABPA and asthma treated with dupilumab. *Clinical and Translational Allergy*. 2021-12. DOI: 10.1002/clt2.12081.

Tjeerd van der Veer; Simone van der Sar-van der Brugge; Marthe S. Paats; Els van Nood; Ingrid C. de Backer; Joachim G.J.V. Aerts; et al. Do-not-intubate status and COVID-19 mortality in patients admitted to Dutch non-ICU wards. *European Journal of Clinical Microbiology & Infectious Diseases*. 2021-10-12. DOI: 10.1007/s10096-021-04223-4.

S.C. Eindhoven; Y. Türk; T. van der Veer; M. Oosterbaan-Beks; B. Goes-de Graaff; S.A. Bendien; et al. Voice bubbling therapy for vocal cord dysfunction in difficult-to-treat asthma – a pilot study. *The Journal of Asthma*. 2020-10-26. DOI: 10.1080/02770903.2020.1837156.

Tjeerd van der Veer; Johannes C.C.M. In 't Veen; Wijnand K. den Dekker; Jelle Miedema. A 79-Year-Old Woman With Dyspnea and Hypoxemia That Worsened in an Upright Position. *Chest*. 2017-12-01. DOI: 10.1016/j.chest.2017.07.004.

Tjeerd van der Veer; Ed Pennings; J.W. Cohen Tervaert; Lindy-Anne Korswagen. Levamisole-contaminated cocaine: a hairy affair. *BMJ Case Reports*. 2015-08-26. DOI: 10.1136/bcr-2015-210970.

T. van der Veer; J.E. Baars; E. Birnie; P. Hamberg. Citation analysis of the 'Big Six' journals in Internal Medicine. *European Journal of Internal Medicine*. 2015-07. DOI: 10.1016/j.ejim.2015.05.017.

Van der Veer T; Frings-Dresen M.H.; Sluiter J.K. Health behaviors, care needs and attitudes towards self-prescription: a cross-sectional survey among Dutch medical students. *PLoS ONE*. 2011. DOI: 10.1371/journal.pone.0028038. PMID: 22132202. PMC: PMC3221693.

About the author

Tjeerd van der Veer was born in August 1986 in Leiden, the Netherlands. He attended primary school in Leiden and graduated from *Adelbert College Wassenaar* in 2005. After a short study of Mechanical Engineering at *Technical University Delft*, he started medical school at *Erasmus University Rotterdam faculty of Medicine* in 2006. During his studies, he pursued coursework the in Philosophy of Science at the *Erasmus School of Philosophy*.

Early in his career, Tjeerd developed a strong interest in respiratory diseases, combining clinical work with research. He gained international experience as an undergraduate researcher in the *University of Florida department of Physiology*, Gainesville, USA and later as a medical intern at *Universidade Vila Velha*, Espírito Santo, Brazil. After graduating in 2013, he worked in the department of internal medicine at the *Sint Franciscus Gasthuis* in Rotterdam, before beginning his residency in pulmonology at the *Franciscus Expertise Centre for Obstructive Lung Disease* in 2014. Having a strong interest in both obstructive and infectious lung diseases, he worked for half a year at the *Tygerberg* hospital at *Stellenbosch University* in Cape Town, South Africa. Inspired by the challenges posed by tuberculosis, he then worked as a researcher at the *Radboud University Medical Center*, working on the development of an e-nose device for tuberculosis screening, before going back to the *Erasmus Medical Center* to finish his pulmonology training.

In 2020, Tjeerd began his PhD research, alongside his role as a pulmonology consultant in the team for pulmonary infectious disease and cystic fibrosis. This position was made possible through the support of the *Erasmus Medical Center department of Pulmonology*, enabling him to conduct both clinical and radiological research, the latter through his involvement in the LungAnalysis lab at *Sophia Children's Hospital*.

Currently, Tjeerd works as a pulmonologist at the *Leiden University Medical Center*, focusing on patients with the genetic disorder alpha-1 antitrypsin deficiency and severe emphysema, as well as translational research in quantitative radiology.