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Machine learning-enhanced HRCT analysis for diagnosis and severity assessment in pediatric asthma

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Introduction

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1. Pediatric asthma: epidemiology and clinical heterogeneity

1.1 Definition and global burden of pediatric asthma

Asthma represents the most common chronic respiratory disease in childhood and remains a major public health concern worldwide. According to estimates from the World Health Organization, asthma affects hundreds of millions of individuals globally, with a substantial proportion of cases occurring during childhood. Pediatric asthma is characterized by recurrent respiratory symptoms, including wheezing, cough, chest tightness, and shortness of breath, associated with variable airflow limitation and airway hyperresponsiveness. Despite advances in diagnosis and treatment, asthma continues to impose a significant burden on children, their families, and healthcare systems. Epidemiological data indicate that the prevalence of pediatric asthma varies considerably across geographic regions, reflecting the complex interplay between genetic susceptibility, environmental exposures, socioeconomic factors, and healthcare access. In high-income countries, asthma prevalence has stabilized or slightly declined in recent years, whereas an increasing trend has been observed in low- and middle-income countries, likely driven by urbanization, air pollution, and lifestyle changes. Regardless of regional differences, asthma remains a leading cause of school absenteeism, emergency department visits, and hospital admissions in children, with a substantial impact on quality of life and psychosocial well-being [1]. Importantly, pediatric asthma is not a single disease entity but rather a heterogeneous condition encompassing a broad spectrum of clinical presentations, disease trajectories, and treatment responses. Most children with asthma achieve adequate symptom control with low-to-moderate doses of inhaled corticosteroids (ICS) and standard controller therapies. However, a subset of patients experiences persistent symptoms, recurrent exacerbations, or functional impairment despite appropriate treatment. This heterogeneity challenges the traditional "one-size-fits-all" approach and underscores the need for refined disease stratification and personalized management strategies. Beyond its immediate clinical manifestations, asthma in childhood may have long-term consequences extending into adult life. Longitudinal cohort studies have demonstrated that impaired lung growth and reduced lung function trajectories established early in life can persist into adulthood, increasing the risk of chronic respiratory morbidity. Children with poorly controlled asthma, particularly those with frequent exacerbations, are more likely to experience accelerated lung function decline, highlighting the importance of early identification and optimal disease control [2]. Within this broad pediatric asthma population, severe asthma represents a distinct and particularly burdensome subgroup that warrants specific attention.

1.2 Severe asthma in children

Severe asthma in children is a relatively rare condition but accounts for a disproportionate share of asthma-related morbidity, healthcare utilization, and costs. Recent high-quality epidemiological evidence has clarified the prevalence of severe asthma within pediatric populations. A systematic review and meta-analysis of European studies estimated that severe asthma affects approximately

3% of children with asthma, although prevalence estimates varied widely depending on the diagnostic criteria applied and the geographical setting [3]. Despite representing a minority of patients, children with severe asthma experience frequent symptoms, recurrent exacerbations, and a markedly reduced quality of life compared with peers with mild or moderate disease. Severe asthma is defined not simply by symptom burden but by the level of treatment required to achieve disease control. According to international recommendations, severe asthma refers to asthma that remains uncontrolled despite optimized therapy with high-dose inhaled corticosteroids combined with additional controller medications, or that becomes uncontrolled when such treatment is reduced [4]. This definition emphasizes the importance of distinguishing truly severe disease from asthma that is difficult to control due to modifiable factors such as poor adherence, incorrect inhaler technique, or untreated comorbidities. The clinical impact of severe asthma in childhood is profound. Children with severe asthma are at increased risk of hospitalizations, emergency department visits, and systemic corticosteroid exposure, which in turn may lead to significant treatment-related adverse effects, including growth impairment and metabolic complications. Moreover, the burden of severe asthma extends beyond physical health, affecting emotional well-being, social participation, and family dynamics. Parents and caregivers often face substantial psychological stress and economic strain related to ongoing disease management and healthcare utilization 3,5. Epidemiological data also suggest variability in the prevalence of severe asthma across regions and according to diagnostic frameworks. In the aforementioned meta-analysis, higher prevalence estimates were observed when Global Initiative for Asthma (GINA) criteria were applied compared with European Respiratory Society (ERS)/American Thoracic Society (ATS) definitions, reflecting differences in ICS dose thresholds and classification approaches [3,4]. These discrepancies highlight the lack of a universally accepted definition of severe asthma in children and complicate comparisons across studies and healthcare systems. From a pathobiological perspective, severe asthma in children is increasingly recognized as a heterogeneous condition encompassing multiple phenotypes and endotypes. Advances over the past decade have improved understanding of the inflammatory and structural mechanisms underlying severe therapy-resistant asthma, including the role of type 2 inflammation as well as non–type 2 pathways [5,6]. Nevertheless, current clinical tools remain insufficient to fully capture this complexity or to reliably predict disease course and treatment response in individual patients. Taken together, these considerations underscore the need for improved strategies to characterize disease severity in pediatric asthma. Beyond symptom-based and functional assessments, there is growing interest in objective markers that reflect underlying structural airway changes and long-term disease burden. In this context, imaging-based approaches and advanced analytical techniques may offer novel insights into the mechanisms and clinical expression of severe asthma in children.

2. Pathophysiology of severe asthma and airway remodeling

2.1 Inflammatory mechanisms in pediatric severe asthma

Asthma is traditionally conceptualized as a chronic inflammatory disease of the airways, characterized by variable airflow obstruction and bronchial hyperresponsiveness. In children, asthma is most commonly associated with type 2 (T2) inflammation, driven by T-helper 2 lymphocytes and innate lymphoid cells type 2, leading to eosinophilic airway inflammation and increased production of cytokines such as interleukin (IL)-4, IL-5, and IL-13. These inflammatory pathways are central to the development of airway hyperresponsiveness, mucus hypersecretion, and acute exacerbations [6]. In severe pediatric asthma, however, inflammation alone does not fully explain disease severity or persistence. Although many children with severe asthma exhibit a T2-high inflammatory profile, mechanistic studies have demonstrated substantial heterogeneity in inflammatory patterns, including eosinophilic, neutrophilic, mixed, and pauci-granulocytic phenotypes [5]. Importantly, these inflammatory phenotypes are not stable over time, and longitudinal studies have shown that airway inflammatory profiles may fluctuate in individual patients, further complicating disease classification. Moreover, the relationship between airway inflammation and clinical severity is often imperfect. Children with severe asthma may experience frequent exacerbations and persistent symptoms despite aggressive anti-inflammatory treatment, including high-dose ICS and systemic corticosteroids. This apparent dissociation suggests that additional pathophysiological mechanisms contribute to disease severity and treatment resistance.

2.2 Steroid resistance and disease persistence

A defining feature of severe asthma is its reduced responsiveness to standard anti-inflammatory therapies. In children with severe therapy-resistant asthma, corticosteroid treatment often fails to fully suppress airway inflammation or achieve sustained disease control. Several mechanisms have been proposed to explain steroid resistance, including altered glucocorticoid receptor signaling, persistent activation of non–T2 inflammatory pathways, and the involvement of structural airway cells in disease pathogenesis [5,7]. Importantly, steroid resistance in pediatric asthma does not necessarily correlate with the absence of inflammation. Studies have shown that children with severe asthma may exhibit ongoing eosinophilic airway inflammation despite systemic corticosteroid treatment, while others demonstrate neutrophilic or mixed inflammatory patterns that are inherently less responsive to corticosteroids [5]. These findings highlight the limitations of relying exclusively on inflammatory biomarkers to assess disease severity or guide treatment escalation. Beyond inflammation, increasing attention has been directed toward the role of airway structural changes in driving persistent airflow limitation and clinical severity. Structural alterations of the airway wall may contribute to fixed airflow obstruction, reduced bronchodilator responsiveness, and long-term impairment of lung function, even in the absence of active inflammation [5].

2.3 Airway remodeling: definition and structural components

Airway remodeling refers to a constellation of structural changes affecting the bronchial wall, including epithelial damage, subepithelial fibrosis, increased airway smooth muscle mass, mucous gland hypertrophy, angiogenesis, and thickening of the reticular basement membrane. These changes alter airway geometry and mechanical properties, leading to increased airway stiffness, luminal narrowing, and heightened susceptibility to airflow limitation. In pediatric asthma, airway remodeling is not merely a late consequence of long-standing disease. Histopathological studies have demonstrated that structural airway changes can be detected early in life, even in preschool children with recurrent wheeze who later develop persistent asthma [5]. By school age, children with severe asthma may exhibit degrees of airway wall thickening and basement membrane remodeling comparable to those observed in adults with long-standing disease [5]. Crucially, airway remodeling appears to progress partially independently of airway inflammation. While inflammatory processes may initiate or amplify remodeling, structural changes can persist despite adequate suppression of inflammation, contributing to ongoing symptoms and functional impairment. This relative autonomy of remodeling from inflammation provides a plausible explanation for the limited efficacy of anti-inflammatory therapies in some children with severe asthma.

2.4 Clinical relevance of airway remodeling in children

The presence and extent of airway remodeling have important clinical implications in pediatric severe asthma. Structural airway changes are associated with persistent airflow limitation, reduced lung function growth, and diminished reversibility to bronchodilators. Longitudinal studies suggest that children with evidence of early airway remodeling are more likely to follow low lung function trajectories into adulthood, increasing the risk of chronic obstructive respiratory disease later in life [2,8]. From a clinical perspective, airway remodeling may represent a key determinant of disease severity that is not adequately captured by symptom scores, spirometry, or inflammatory biomarkers. Indeed, children with severe asthma may display relatively preserved spirometric indices despite significant structural abnormalities, particularly in the small airways. This dissociation underscores the limitations of conventional functional assessments in reflecting the true burden of airway disease. Furthermore, airway remodeling may influence treatment response. Increased airway smooth muscle mass and wall thickness can reduce the effectiveness of bronchodilators and contribute to fixed airflow obstruction, while fibrotic changes may limit the reversibility of disease even with optimal anti-inflammatory therapy [5]. These factors highlight the need for diagnostic tools capable of directly assessing airway structure in vivo.

2.5 Implications for disease assessment and research

Taken together, current evidence indicates that severe asthma in children is a complex, multifactorial disease in which inflammation and airway remodeling interact but are not synonymous. While inflammation remains a key therapeutic target, structural airway changes represent a distinct and clinically relevant dimension of disease severity. Despite their importance, airway remodeling processes are difficult to assess in routine clinical practice. Invasive techniques such as bronchial biopsy provide direct histological information but are unsuitable for widespread or longitudinal use in children [5,9]. As a result, there is a critical unmet need for non-invasive methods that can quantify airway structural changes and serve as surrogate markers of remodeling. This gap in assessment tools has stimulated growing interest in imaging-based approaches, particularly high-resolution computed tomography, as a means of visualizing and quantifying airway wall abnormalities in pediatric severe asthma. When combined with advanced analytical techniques, such as quantitative image analysis and machine learning (ML), imaging has the potential to bridge the gap between pathophysiology and clinical phenotyping, enabling a more comprehensive assessment of disease severity.

3. Current tools for assessing disease severity in pediatric asthma

3.1 Clinical assessment and symptom-based evaluation

In routine clinical practice, the assessment of asthma severity in children relies primarily on clinical evaluation, including symptom frequency, exacerbation history, and the level of treatment required to maintain disease control. International guidelines define asthma severity retrospectively, based on the intensity of therapy needed to achieve adequate control, rather than on a single cross-sectional measurement [10]. This approach reflects the dynamic nature of asthma and the variability of symptoms over time. Symptom-based tools, such as validated asthma control questionnaires, provide a standardized method for evaluating daily symptoms, activity limitation, and nocturnal awakenings. In children with severe asthma, however, symptom perception may be unreliable. Poor symptom awareness, particularly in younger children and adolescents, can lead to underestimation of disease severity, while psychosocial factors may amplify symptom reporting independently of underlying airway pathology. Moreover, symptom scores are inherently subjective and may be influenced by environmental exposures, adherence patterns, and comorbid conditions [6]. Exacerbation frequency is another key clinical marker of severity. Severe asthma is characterized by recurrent exacerbations requiring systemic corticosteroids, emergency department visits, or hospital admissions [4,10]. Although a history of previous exacerbations is one of the strongest predictors of future risk, exacerbations are episodic events and do not necessarily reflect the chronic structural burden of disease. Children may experience significant airway pathology even during periods of apparent clinical stability.

3.2 Lung function testing

Objective assessment of lung function is a cornerstone of asthma management and severity evaluation. Spirometry, including measurements of forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and the FEV_1/FVC ratio, is widely used to assess airflow limitation and bronchodilator responsiveness [6]. In pediatric severe asthma, reduced lung function and incomplete reversibility after bronchodilation are associated with worse outcomes and increased disease burden. Despite its central role, spirometry has important limitations in children with severe asthma. First, spirometric indices may remain within normal ranges in a substantial proportion of children with clinically severe disease, particularly between exacerbations. Second, spirometry predominantly reflects large airway function and may be insensitive to early or localized changes in the small airways, where remodeling processes are thought to play a major role. Third, lung function measurements are effort-dependent and may be challenging to perform reliably in younger children. Longitudinal studies have shown that lung function trajectories established early in life tend to track into adulthood, underscoring the prognostic value of spirometry [8]. However, spirometry alone provides limited insight into the mechanisms underlying airflow limitation and does not directly assess airway wall structure or remodeling processes.

3.3 Biomarkers of airway inflammation

Biomarkers of airway inflammation are increasingly used to support the assessment of asthma severity and guide treatment decisions. Commonly used biomarkers in pediatric asthma include blood eosinophil counts, total serum IgE, and fractional exhaled nitric oxide (FeNO). These markers are particularly useful for identifying type 2 inflammatory pathways and selecting candidates for targeted biological therapies [6]. In children with severe asthma, inflammatory biomarkers have demonstrated clinical utility but also significant limitations. Elevated eosinophil counts and FeNO levels are associated with increased exacerbation risk and may predict response to corticosteroids and biologic agents. However, these biomarkers exhibit substantial intra-individual variability and may be influenced by recent treatment, infections, or environmental exposures. Importantly, inflammatory biomarkers do not provide direct information on airway structure or the extent of remodeling. Children with severe asthma may exhibit persistent symptoms and airflow limitation despite low or suppressed inflammatory marker levels, particularly in the context of high-dose anti-inflammatory therapy. Conversely, elevated biomarkers may be present in children with relatively preserved lung function and minimal structural disease. This dissociation limits the ability of inflammatory markers to serve as comprehensive indicators of disease severity [5,6].

3.4 Assessment of comorbidities and modifiable factors

A critical component of severity assessment in pediatric asthma involves the systematic evaluation of comorbidities and modifiable factors that may contribute to poor disease control. Conditions such as allergic rhinitis, obesity, dysfunctional breathing, gastroesophageal reflux, and psychosocial stressors are common in children with difficult-to-treat asthma and may mimic or exacerbate asthma symptoms[7]. International consensus documents emphasize the importance of a structured, multidisciplinary assessment to distinguish true severe therapy-resistant asthma from asthma that appears severe due to remediable factors. In many children, optimization of adherence, inhaler technique, and comorbidity management leads to substantial improvement in control, allowing treatment de-escalation. Only a subset of patients remains uncontrolled despite optimal management and meets criteria for severe asthma. While this comprehensive approach is essential, it does not directly address the assessment of airway pathology. Even after modifiable factors have been corrected, current tools provide limited insight into the structural substrate of disease in children with persistent severe asthma.

3.5 Invasive assessment techniques and their limitations

Direct assessment of airway inflammation and remodeling can be achieved through invasive techniques such as bronchoscopy with bronchoalveolar lavage and endobronchial biopsy. These methods provide valuable mechanistic information and have contributed significantly to understanding the pathophysiology of severe asthma in children. However, invasive procedures are associated with ethical, practical, and safety considerations that limit their use in routine clinical practice, particularly in pediatric populations. Bronchoscopy is typically reserved for selected cases and is unsuitable for repeated or longitudinal assessment [5,9]. As a result, invasive techniques cannot serve as practical tools for ongoing severity evaluation or treatment monitoring in children with severe asthma.

3.6 Unmet needs in severity assessment

Taken together, current tools for assessing disease severity in pediatric asthma - clinical evaluation, lung function testing, inflammatory biomarkers, and invasive investigations - each provide valuable but incomplete information. None of these approaches alone captures the full complexity of severe asthma or adequately reflects the burden of airway structural disease. In particular, there is a critical gap in the non-invasive assessment of airway remodeling, a key determinant of persistent airflow limitation and long-term outcomes. This gap limits the ability to stratify patients based on underlying pathology, to monitor disease progression, and to evaluate the impact of emerging therapies on structural airway changes. These limitations highlight the need for complementary approaches that can directly assess airway structure in vivo. Imaging-based techniques, and especially high-resolution computed tomography combined with quantitative analysis, offer a promising avenue to address this unmet need and to enhance the assessment of disease severity in pediatric asthma.

4. Role of chest imaging and high-resolution computed tomography in pediatric severe asthma

Chest imaging is not routinely indicated for the diagnosis or day-to-day management of childhood asthma, which primarily relies on clinical history, symptom control, and pulmonary function testing. Nevertheless, in children with severe asthma or difficult-to-treat disease, imaging - particularly high-resolution computed tomography (HRCT) - has a distinct and increasingly relevant role [11,12,13]. The rationale is that severe asthma is structurally and functionally heterogeneous across the lung, and this regional heterogeneity is only partially captured by global physiological measures (e.g., FEV_1) or symptoms. Imaging can therefore provide complementary information by (i) excluding alternative diagnoses and identifying comorbidities that may mimic or perpetuate uncontrolled asthma, (ii) characterizing structural airway and parenchymal abnormalities, and (iii) enabling quantitative metrics that may support phenotyping, risk stratification, and, in selected contexts, treatment monitoring.

4.1 Clinical indications of HRCT in severe/difficult-to-treat pediatric asthma

In pediatric practice, the classical indication for CT has been to “rule out” alternative diagnoses in children with atypical presentations, recurrent severe exacerbations, persistent symptoms despite optimized therapy, discordant clinical and functional findings, or suspicion of complications such as bronchiectasis or allergic bronchopulmonary aspergillosis. This framework is emphasized in pediatric perspectives that note CT is usually performed in children with asthma to exclude alternative diagnoses, while also acknowledging that technical advances allow HRCT to assess airway wall thickening and to evaluate small-airway involvement indirectly through low-attenuation areas (air trapping). Beyond differential diagnosis, HRCT may contribute to assessing airway remodeling in children in whom invasive gold standards (bronchoscopy, bronchoalveolar lavage, and biopsy) are not suitable for routine or longitudinal use, and in whom indirect inflammatory biomarkers have limited ability to reflect the regional burden of structural disease. A dedicated pediatric discussion of imaging in severe childhood asthma underscores that, despite feasibility, unresolved issues related to reconstruction algorithms, imaging parameters, and applicability in younger children constrain routine implementation; accordingly, HRCT is unlikely to be used broadly for monitoring but may be appropriate in severe asthma. A critical practical implication is that HRCT provides maximal clinical value when the question is explicit (e.g., detection of bronchiectasis, characterization of air trapping, documentation of substantial airway wall abnormality) and when imaging results are likely to influence subsequent management. This targeted approach aligns with imaging-biomarker frameworks positioning CT as one component of multidimensional phenotyping that integrates clinical, functional, inflammatory, and structural domains.

4.2 What HRCT "sees" in severe asthma: the structural–functional interface

HRCT provides high spatial resolution of airway and parenchymal morphology and, when acquired at different lung volumes (typically inspiratory and expiratory acquisitions), yields indirect functional information related to ventilation heterogeneity and small-airway dysfunction. The structure–function paradigm is central to contemporary asthma imaging: regional abnormalities such as air trapping and mucus plugging can be quantified, related to clinical traits, and—in research settings—linked to outcomes and endotypes. In pediatric severe asthma, the most clinically relevant HRCT domains include:

- Proximal airway remodeling surrogates (e.g., bronchial wall thickening; airway wall thickness and wall area metrics);
- Indirect markers of small-airway disease (e.g., expiratory air trapping; low-attenuation areas; mosaic attenuation);
- Luminal obstruction by mucus (mucus plugging), increasingly recognized as a clinically meaningful "treatable trait";
- Bronchiectasis and other structural abnormalities, which may alter management and prompt additional etiological evaluation.

These domains frequently coexist and may define distinct "imaging phenotypes" with potential prognostic relevance.

4.3 Airway wall thickening and remodeling: pediatric evidence and interpretation

Bronchial wall thickening (BWT) is among the most commonly reported HRCT findings in pediatric asthma cohorts and is often interpreted as a surrogate of chronic inflammation and/or remodeling. Early thin-section CT work in children with stable moderate-to-severe asthma demonstrated the presence of BWT even during clinically stable periods, suggesting that the finding cannot be attributed solely to acute bronchoconstriction and supporting a structural component consistent with persistent airway pathology.A prospective pediatric HRCT study in difficult-to-treat asthma proposed a pragmatic scoring approach based on the number of visible bronchi and showed significantly higher BWT scores in difficult-to-treat asthma compared with controls, while correlations with conventional spirometric indices were limited. Importantly, the authors concluded that HRCT evidence of BWT may constitute an additional criterion of asthma severity in children and might help identify those at higher risk of remodeling. Two implications are particularly relevant in severe pediatric disease. First, structural abnormalities may be present despite modest or variable spirometric impairment, reflecting the imperfect coupling between global flow limitation and regional airway pathology in children. Second, quantification is central: while qualitative interpretation of BWT is clinically informative, quantitative airway metrics (e.g., wall thickness [WT], wall area [WA], and size-adjusted measures WT% and WA%) offer greater potential for reproducibility and integration into longitudinal analyses and computational pipelines.

4.4 Small-airway disease and air trapping: HRCT as a regional biomarker

Small-airway dysfunction is a key driver of morbidity in severe asthma and is particularly relevant to pediatric disease trajectories, given the potential for early-life airway injury and long-term fixed obstruction. HRCT cannot directly visualize the smallest airways; therefore, expiratory air trapping and low-attenuation areas (LAA) function as indirect, regional surrogates of small-airway involvement. Pediatric discussions have emphasized that inspiratory and expiratory HRCT acquisitions can capture low-density areas believed to represent air trapping and that such measures may correlate with indices of small-airway functional impairment. More recent quantitative pediatric evidence strengthens the clinical relevance of air trapping. In a retrospective pediatric cohort (5–17 years) with severe asthma compared with controls, children with severe asthma had substantially higher mean air trapping index (AT%) and higher airway wall thickness metrics. AT% showed very strong negative correlations with FVC and FEV_1 and was higher in those with previous asthma-related hospitalizations, linking a quantitative imaging marker of small-airway disease to clinically meaningful severity indicators. These data support air trapping quantification as an informative imaging domain in pediatric severe asthma and provide a mechanistic bridge between regional ventilation heterogeneity and clinical outcomes, particularly in children where spirometric impairment may not fully reflect the burden of peripheral airway disease.

4.5 Bronchiectasis and other structural abnormalities: prevalence and management implications in children

Bronchiectasis is a high-impact finding in pediatric severe asthma because it may indicate chronic airway injury, contribute to recurrent symptoms and infections, and prompt additional diagnostic work-up and targeted interventions. In a selected cohort of children with severe/difficult asthma, bronchiectasis was identified in 27% of patients, with increasing extent/severity correlating with age; abnormal CT findings were highly prevalent, and bronchiectasis was present in approximately one third of the cohort. This prevalence supports a pragmatic conclusion: although HRCT should not be routine in pediatric asthma due to radiation exposure, selected severe-asthma populations may have a sufficiently high prevalence of management-relevant structural abnormalities (including bronchiectasis) to justify imaging when clinical suspicion is appropriate.

4.6 Mucus plugging: a treatable structural trait and the link to functional imaging

Mucus plugging has emerged as a particularly compelling imaging phenotype in severe asthma because it provides a direct structural mechanism for airflow obstruction and ventilation heterogeneity and has potential therapeutic implications. CT-based mucus scoring systems (e.g., segment-based scoring) enable semi-quantitative assessment of plug burden, and advanced algorithms increasingly support automated detection and characterization. Integration of CT mucus assessment with functional imaging offers a powerful structure–function model. In severe asthma, CT-quantified mucus plugging was evaluated alongside MRI-derived ventilation defect percent (VDP), demonstrating that mucus plugs contribute to ventilation heterogeneity and that mucus burden correlated with pre- and post-bronchodilator Longitudinal evidence further supports mucus plugging as a clinically meaningful phenotype. In a longitudinal cohort analysis, mucus plugs persisted over time, and changes in mucus plug burden were associated with changes in airflow obstruction, suggesting that mucus is not merely an epiphenomenon but may contribute to sustained impairment. The synthesis of these observations supports positioning mucus plugging as an imaging-derived "treatable trait" in severe asthma and provides a rationale for incorporating mucus assessment into quantitative imaging frameworks.

4.7 Quantitative CT (qCT): from qualitative patterns to reproducible biomarkers

The shift from qualitative HRCT interpretation to quantitative CT (qCT) is a defining trend in asthma imaging and is highly relevant for severe asthma, where heterogeneity limits the utility of single global measures. Imaging-biomarker frameworks argue that CT-derived airway and density measurements can correlate with clinical severity and pathology while enabling phenotypic stratification. In qCT, airway remodeling is commonly operationalized using measures such as WT/WA and their size-adjusted counterparts (WT%/WA%), which are intuitive surrogates of remodeling and have been associated with severity in broader severe-asthma literature, providing a strong conceptual basis even when pediatric histologic correlation is limited. Density-based analyses quantify hyperinflation and air trapping using thresholds and, increasingly, voxel-wise co-registration approaches such as parametric response mapping (PRM) and disease probability mapping (DPM) to refine attribution to small-airway disease. Associations between qCT metrics and longitudinal outcomes have been reported in severe adult asthma cohorts, supporting the concept that imaging-derived structural and functional metrics may have prognostic utility at the cohort level. In SARP-3, baseline qCT measures reflecting greater airway remodeling and small-airway disease/hyperinflation were associated with future lung function decline and exacerbations. These findings are consistent with contemporary commentaries emphasizing the emerging role of quantitative imaging in phenotype/endotype characterization and prognosis, while highlighting the need for additional work in automation, standardization, and radiation minimization.

4.8 Automation, AI, and translational relevance in pediatric severe asthma

Translation of qCT into scalable workflows requires robust and reproducible feature extraction, which is computationally intensive and sensitive to acquisition parameters, segmentation choices, and reconstruction settings. Consequently, automation and computational approaches are increasingly viewed as prerequisites for broad adoption. Contemporary imaging perspectives emphasize the need for automated, standardized pipelines and reporting to enable clinical translation of quantitative imaging biomarkers. In pediatric severe asthma, computational imaging is particularly attractive because it can reduce observer dependence, facilitate extraction of multiple complementary metrics (airway morphometry, air trapping, mucus burden, bronchiectasis), and support integrated models that combine imaging with clinical and functional data—an approach that is directly aligned with modern severe-asthma phenotyping strategies.

4.9 Methodological considerations and pediatric-specific constraints: standardization and radiation stewardship

Across pediatric and adult imaging literature, HRCT's potential is limited by methodological variability. Pediatric perspectives explicitly note unresolved questions about reconstruction validity, imaging parameters, and applicability in younger children. Modern quantitative imaging commentaries similarly call for standardized protocols and reporting and for minimizing radiation exposure as prerequisites for broader adoption. In pediatric severe asthma, these constraints translate into pragmatic requirements:

- Indication-driven imaging: HRCT should be performed when expected diagnostic or phenotyping yield justifies radiation exposure and when results can influence management.
- Low-dose optimization: acquisition parameters should be tailored to minimize dose while preserving interpretability and quantitative integrity, especially for research protocols.
- Lung-volume control: inspiratory and expiratory acquisitions improve assessment of air trapping and density-based metrics but can be challenging in children; feasibility and reproducibility should be addressed explicitly in protocol design.
- Interoperability for qCT/automation: standardization across scanners, kernels, slice thickness, and reconstruction pipelines is essential to ensure that automated biomarkers remain comparable across sites and time.

4.10 Summary and rationale for subsequent work

In summary, HRCT in pediatric severe asthma has evolved from a modality primarily used to exclude alternative diagnoses to a tool capable of characterizing clinically meaningful structural and regional functional traits. These include airway wall thickening (a remodeling surrogate), expiratory air trapping (a proxy of small-airway disease), mucus plugging (a treatable trait linked to ventilation heterogeneity and longitudinal airflow impairment), and bronchiectasis (a management-relevant abnormality with notable prevalence in selected pediatric severe cohorts). At the same time, pediatric-specific constraints—radiation exposure, protocol standardization, and feasibility of lung-volume controlled acquisitions—mandate careful patient selection and methodological rigor. Collectively, these considerations provide the scientific and methodological rationale for investigating quantitative HRCT-derived markers, and for evaluating computational approaches that can integrate multi-domain imaging information to support diagnosis and severity assessment in pediatric severe asthma in subsequent chapters.

5. Rationale and objectives of the original research

The preceding section outlined how HRCT can characterize clinically meaningful structural and regional functional traits in severe asthma, including airway wall thickening as a surrogate of remodeling, air trapping as an indirect marker of small-airway dysfunction, mucus plugging as a potentially treatable structural trait, and bronchiectasis as a management-relevant abnormality in selected pediatric cohorts. While these HRCT features have been consistently described, their translation into operational biomarkers that can support diagnostic evaluation and severity assessment in children has been limited by several factors: (i) the rarity of pediatric severe asthma and the consequent small sample sizes in single-center studies; (ii) heterogeneity of acquisition protocols and reconstruction parameters, which constrains comparability across sites; (iii) inter-observer variability for qualitative or semi-quantitative readings; and (iv) the absence of sensitive, validated quantitative models that can integrate multiple imaging traits into an interpretable decision framework for clinicians. Within this landscape, computational analysis and ML provide a methodological opportunity. HRCT generates high-dimensional data with potentially non-linear relationships among airway morphometry, parenchymal abnormalities, and categorical findings (e.g., bronchiectasis, mucus plugging). ML approaches can be used to identify the most informative imaging traits, quantify their relative importance, and build predictive models that are cross-validated to reduce overfitting in small datasets. At the same time, a clinically useful model must remain transparent and interpretable, particularly in pediatrics where imaging is performed selectively and results are expected to inform downstream decisions rather than replace clinical judgment.

5.1 Study rationale

The original research presented in this thesis was designed to address a practical and clinically relevant question: whether a structured and computationally supported HRCT assessment could reliably discriminate children with severe asthma from non-asthmatic controls and, in doing so, identify a parsimonious set of imaging traits reflecting airway remodeling and severe structural phenotypes. This rationale is supported by prior pediatric quantitative CT evidence suggesting that airway wall measures (e.g., AWT and AWT%) and air trapping indices can differ between children with severe asthma and healthy controls, and that these quantitative parameters may correlate with functional impairment and clinically meaningful outcomes such as prior hospitalizations. Additionally, the pediatric literature indicates that bronchiectasis can be detected in a substantial minority of children referred for severe/difficult asthma evaluation, reinforcing the potential value of HRTC.

In parallel, adult severe asthma studies integrating CT-based mucus quantification with functional imaging demonstrate that luminal obstruction by mucus can be a dominant contributor to ventilation heterogeneity and airflow limitation, supporting mucus plugging as a mechanistically anchored imaging trait. Taken together, these data justify a research strategy centered on the extraction and integration of airway wall measures and categorical structural abnormalities from HRCT as candidate markers of severe pediatric disease.

5.2 Study design overview

A retrospective case–control design was adopted, comparing children with severe asthma, defined according to ERS/ATS criteria, to age- and sex-matched controls without asthma who had undergone HRCT for non-asthma-related clinical indications. Children with severe asthma were identified within a dedicated pediatric severe asthma clinic and included if they were 6–17 years of age and had undergone HRCT as part of a standardized clinical assessment pathway. Exclusion criteria were applied to avoid confounding by diseases that mimic severe asthma or independently alter airway structure, including cystic fibrosis, primary ciliary dyskinesia, and tracheobronchomalacia; analogous exclusions were used for controls to ensure the absence of relevant respiratory diseases or bronchiectasis. HRCT examinations were acquired using a dedicated low-dose volumetric protocol at full inspiration (total lung capacity). Imaging interpretation included both quantitative airway morphometry and qualitative/semi-quantitative scoring of key structural findings. A structured set of airway parameters was measured on reconstructed thin sections orthogonal to the airway axis, including bronchial lumen area (BLA), wall area (WA), airway wall thickness (AWT) and airway wall thickness percentage (AWT%), airway diameters, and the wall-area to lumen-area ratio (WA/LA). In addition, categorical/semi-quantitative features were assessed, including bronchial thickening (BT score), bronchiectasis (grading and severity), mucus plugging, emphysema patterns, and selected parenchymal abnormalities.

5.3 Primary and secondary objectives

Primary objective: To develop and internally validate a ML–assisted HRCT analysis framework capable of discriminating children with severe asthma from non-asthmatic controls, and to identify the imaging features with the greatest predictive contribution to this classification.

Secondary objectives:

- To quantify differences in airway remodeling surrogates and structural abnormalities between severe asthma and controls across a predefined set of imaging traits (e.g., BT score, AWT%, bronchiectasis measures, mucus plugging, emphysema patterns).
- To compare the performance of complementary modeling strategies—classification trees, random forests, and conventional ROC-based thresholding—using rigorous internal validation procedures (leave-one-out cross-validation, LOOCV) appropriate for small sample sizes.
- To derive an interpretable imaging-based severity classifier that could serve as a candidate radiological marker of severe pediatric asthma, acknowledging the need for future external validation.

5.4 Working hypothesis and expected contribution

The underlying hypothesis was that quantitative markers of airway remodeling, particularly airway wall thickness expressed relative to airway size (AWT%), together with selected categorical structural traits (e.g., bronchial thickening, bronchiectasis, mucus plugging) would distinguish children with severe asthma from controls with high accuracy. Consistent with this rationale, the classification results demonstrated that HRCT scans differentiated severe asthma from controls, with severe asthma associated with higher bronchial thickening scores, increased AWT%, higher bronchiectasis grading/severity scores, and the presence of mucus plugging and centrilobular emphysema. In the modeling framework, AWT% emerged as the most informative predictor: conventional ROC analysis identified an AWT% threshold ($\geq$ 38.6) as an optimal discriminator, and both tree-based and ensemble methods achieved high cross-validated performance in this dataset. These findings support the concept that a parsimonious, quantitatively anchored imaging marker may capture a dimension of severe pediatric asthma that is not fully represented by routine functional testing.Finally, methodological constraints inherent to pediatric imaging remain central in interpreting and generalizing these results. In particular, the absence of expiratory scans prevents direct quantitative assessment of air trapping in this cohort, limiting the ability to fully characterize small-airway dysfunction using density-based metrics and highlighting a priority area for future protocol optimization within radiation stewardship principles.

6. Materials and Methods

6.1 Study design, setting, and ethical approval

A retrospective case–control study was conducted within the Pediatric Severe Asthma Clinic of Fondazione IRCCS Policlinico San Matteo (Pavia, Italy). The study followed the STROBE recommendations for observational research and was approved by the local Ethics Committee (approval number 2021-3.1/454). The protocol was registered on ClinicalTrials.gov (NCT05140889).

6.2 Study population

6.2.1 Severe asthma group

Children and adolescents who underwent chest HRCT as part of a standardized clinical assessment pathway between 2009 and 2022 were screened. Eligibility criteria were: age 6–17 years and a confirmed diagnosis of severe asthma according to ERS/ATS criteria. Conditions potentially mimicking severe asthma were excluded, including (but not limited to) cystic fibrosis, primary ciliary dyskinesia, and tracheobronchomalacia.

6.2.2 Control group

Controls were age- and sex-matched pediatric subjects who underwent HRCT for clinical reasons unrelated to asthma and had no history of asthma or chronic respiratory symptoms. Exclusion criteria for controls included any respiratory disease or imaging-relevant condition capable of altering lung structure (including bronchiectasis), in order to minimize confounding due to pre-existing abnormalities.

6.3 Clinical, functional, and biological data collection

For participants in the severe asthma group, demographic and clinical variables were obtained from medical records, including age, sex, ethnicity, age at symptom onset, age at asthma diagnosis, comorbidities, and maintenance therapy. Markers of type-2 inflammation and atopy were collected when available, including specific IgE sensitizations, total serum IgE, and peripheral blood eosinophil counts. Data on disease burden and severity proxies were also extracted, including oral corticosteroid use, asthma-related emergency department visits, and hospitalizations.

6.4 Lung function assessment

Spirometry was performed in accordance with ATS/ERS standards using a calibrated spirometer; the best value among three technically acceptable manoeuvres was recorded. Bronchodilator responsiveness was calculated as the percent change in FEV_1 following administration of salbutamol 400 mcg, and considered positive when meeting conventional thresholds (increase ≥12% and ≥200 mL in FEV_1). FeNO was collected as part of the functional assessment when available.

6.5 HRCT acquisition protocol

6.5.1 Scan acquisition and reconstruction

HRCT examinations were acquired on a 64-section multidetector CT system (Aquilion Toshiba One) at full inspiration (total lung capacity) using a dedicated low-dose volumetric protocol. Scans were obtained cranio-caudally with helical acquisition and without intravenous contrast. Key parameters included tube voltage 100–120 kV, tube current 50–60 mAs, collimation 0.75 mm, reconstruction slice thickness 1 mm, reconstruction interval 1 mm, and a 512×512 matrix. A high-spatial-frequency algorithm was used to optimize spatial resolution; images were reviewed using a parenchymal window setting (width 1800 HU, level −600 HU) and a patient-adapted field of view (approximately 15–35 cm).

6.5.2 Quality and dose considerations for quantitative CT in pediatrics

Given the pediatric context, HRCT was performed only when clinically justified and within low-dose constraints. Quantitative CT outputs are sensitive to acquisition factors such as kVp, mAs, reconstruction kernels, and breath-hold lung volume; therefore, protocol consistency and careful patient coaching are critical to reduce measurement variability and to preserve interpretability of densitometric and morphometric indices. In quantitative lung CT research, lower-dose strategies are commonly implemented by selecting reduced mAs while maintaining a consistent kVp across subjects, as changes in kVp affect attenuation values independently of disease.

6.6 CT image analysis

6.6.1 Reading workflow and software environment

All HRCT examinations were independently reviewed by two experienced radiologists using the COPD application within IntelliSpace Portal (release 9; Philips Medical Systems). The platform supports lung volume computation, reconstruction of thin sections orthogonal to the airway axis, and semi-automatic measurement of airway dimensions; these functionalities were leveraged to standardize morphometric outputs across subjects.

6.6.2 Quantitative airway morphometry

A comprehensive set of airway parameters was recorded, including bronchial lumen area (BLA), wall area (WA), airway wall thickening (AWT), multiple lumen and airway diameters (average, maximal, effective), and the wall area to lumen area ratio (WA/LA). Bronchial generation was estimated using the Weibel model (trachea as generation 0 with increments after each bifurcation). For normalization, measurements were adjusted for anthropometric indices including body mass index and body surface area, as appropriate for pediatric scaling.

6.6.3 Semi-quantitative scoring of airway abnormalities and comorbid structural findings

In addition to continuous airway metrics, a structured evaluation of key imaging features relevant to severe asthma was performed (Table 1):

- Bronchial thickening (BT score): semi-quantitative scoring of thickening in identifiable segmental and subsegmental bronchi. Scores were assigned per lobe (including lingula) and aggregated into an overall score.

- Airway wall thickening (AWT categorical score): graded in relation to the diameter of the accompanying vessel, from normal/minimal thickening to thickening exceeding vessel diameter.
- Bronchiectasis grading and severity: bronchiectasis extent was categorized (localized vs extensive vs generalized cystic), and severity was classified by morphological pattern (cylindric vs varicose/cystic). Scores were assigned per lobe and combined into global indices.
- Bronchial–arterial ratio (BA ratio): computed by dividing the average bronchial lumen diameter (at right B1 and right B10) by the diameter of the accompanying artery at segmental/subsegmental level; values beyond prespecified thresholds were considered abnormal.
- Additional lung findings: mucus plugging, emphysema (and pattern classification), and parenchymal abnormalities (e.g., ground-glass opacities, consolidation, collapse) were assessed according to predefined criteria.

Table 1. Scoring System for CT images

BT score	**Findings of AWT**	**BE grading score**	**Extent of BE**	**BE severity score**	**Finding of BE**
0	Normal AWT	0	No disease	0	Absence of bronchial dilatation
1	Minimal AWT	1	Localized bronchiectasis affecting one or part of one bronchopulmonary segment (localized)	1	Mild (cylindric)
2	AWT equivalent to 50% of the diameter of the adjacent blood vessel	2	Bronchiectasis in more than one bronchopulmonary segment (extensive)	2	Severe (varicose and cystic bronchial dilatation)
3	AWT equivalent from 50% to 100%of the diameter of the adjacent vessel	3	Generalized cystic bronchiectasis		
4	AWT greater than 100% the diameter of the adjacent vessel				

Scores were assigned independently for each lobe e for each lung (right upper, right middle, right lower, left upper, lingula and left lower). The scores of every lobe were combined to create an overall score for each CT parameter.AWT: Airway wall thickening; BE: Bronchiectasis; BT: Bronchial thickening.

The lobar-based approach (five lobes plus lingula) and independent readings aimed to maximize reproducibility of both continuous morphometry and ordinal scores—an aspect that has been historically emphasized in pediatric

6.7 Outcomes

The primary analytical objective was to determine whether HRCT-derived airway and lung structural features could discriminate children with severe asthma from non-asthmatic controls, and to identify the subset of imaging variables most strongly associated with severe asthma status.

6.8 Statistical analysis and machine-learning framework

6.8.1 Descriptive and univariate analyses

Continuous variables were summarized using mean and standard deviation, while categorical variables were reported as absolute and relative frequencies. Between-group comparisons were performed using non-parametric tests for continuous variables and exact tests for categorical variables, reflecting the sample size and distributional considerations typical of pediatric severe asthma cohorts.

6.8.2 Supervised classification models

Three classifiers were trained to discriminate severe asthma from controls using radiological variables as predictors:

- Classification tree: sequential binary splits partitioned the predictor space into regions associated with the outcome. To limit overfitting, the tree complexity parameter was selected to maximize leave-one-out cross-validation (LOOCV) accuracy.
- Random forest: an ensemble of decision trees trained on bootstrap samples, combined to produce consensus predictions and reduce the instability and "masking" limitations of single trees. A random subset of predictors was selected at each split (M fixed during model tuning).
- Receiver operating characteristic (ROC) analysis: a conventional ROC framework was used to evaluate single-predictor discrimination and derive an optimal binary classifier based on threshold selection.
- Model performance was quantified using sensitivity, specificity, and accuracy, estimated both in training data and under LOOCV to provide a conservative internal validation in the context of limited sample size.

6.9 Data governance and reproducibility

All data were handled in accordance with ethical approvals and institutional requirements. Imaging analyses were conducted on de-identified datasets, and the study dataset was retained under controlled access; data availability was defined according to institutional and publication policies.

7. Results

7.1 Study population and clinical characteristics

A total of 41 children were included: 20 with severe asthma (SA) and 21 non-asthmatic controls. The SA group comprised 40% females with a mean age of 10.4 years, while controls comprised 48% females with a mean age of 11.4 years. Baseline characteristics were comparable between groups, with no statistically significant differences in body mass index (BMI) z-score ($p = 0.141$) or ethnicity ($p = 0.067$). Overall, 20% of participants were exposed to passive smoking and 30% reported domestic pet exposure (Table 2). Within the SA group, the mean age at onset of asthma symptoms was 5.7 years, and the mean interval between symptom onset and medical diagnosis of severe asthma was 4.7 years. Disease control was classified as uncontrolled in 70% of patients, and 95% reported current asthma symptoms. Sensitization to at least one aeroallergen was documented in 70% of cases (predominantly house dust mite), with a mean total IgE level of 1165.6 IU/mL and a mean blood eosinophil count of 464 cells/μL. Relevant comorbidities included allergic rhinitis

(35%), food allergy history (40%), atopic dermatitis (25%), and obesity (25%). Lung function in the SA cohort showed a mean pre-bronchodilator FEV_1 of 84.9% predicted (z-score −1.11), mean FVC of 98.7% predicted (z-score −0.16), and mean FEV_1/FVC of 83.6% (z-score −1.78). Mean bronchodilator responsiveness was 12.5%. Regarding exacerbation burden, the mean number of lifetime hospitalizations for asthma was 2; 35% had a history of at least one hospital admission and 45% had at least one emergency department visit in the preceding 12 months. During acute exacerbations, 90% of children received oral corticosteroids for at least 3 days.

Table 2. Participant characteristics by disease status.

	Controls N (%)	Severe asthmatics N (%)	p-value
Female gender	10 (48)	8 (40)	0.756
Age (yrs)	11.4 (3.2)	10.4 (4.1)	0.454
Ethnicity			0.067
Caucasian	19 (90)	13 (65)	
African	2 (10)	7 (35)	
BMI (kg/m^2)	18.9 (2.8)	20.7 (4.6)	0.141
Current passive smoke exposure	N.A.	4 (20)	-
Comorbidities			-
Allergic rhinitis	N.A.	7 (35)	-
Food allergy	N.A.	8 (40)	-
Obesity	N.A.	5 (25)	-
Chronic rhinosinusitis with nasal polyps	N.A.	2 (10)	-
Atopic dermatitis	N.A.	5 (25)	-
Lifetime hospitalizations for asthma (No.)	N.A.	2.0 (1.7)	-
Hospitalizations/ED visits, previous 12 months			-
No	N.A.	4 (20)	
ED visits	N.A.	9 (45)	
Hospitalizations	N.A.	7 (35)	
Patients requiring oral steroids in the last 12 months for asthma exacerbations	N.A.	18 (90)	-
Current asthma symptoms	N.A.	19 (95)	-
Total IgE (IU/ml)	N.A.	1165.6 (1042.4)	-
Allergic sensitization at least one aeroallergen	N.A.	14 (70)	-
Eosinophil count (cells/mcl)	N.A.	464.0 (331.4)	-
Exhaled nitric oxide (ppb)	N.A.	61.8 (56.2)	-
FEV_1 z-score	N.A.	-1.11 (1.87)	-
FVC z-score	N.A.	-0.16 (1.58)	-
FEV_1/FVC z-score	N.A.	-1.78 (0.80)	-
FEF_{25-75} z-score	N.A.	-1.48 (1.20)	-
FEF_{75} z-score	N.A.	-1.03 (1.52)	-
Bronchodilator responsiveness (%)	N.A.	12.5 (11.4)	-
Asthma control status			-
Partly controlled	N.A.	6 (30)	-
Uncontrolled	N.A.	14 (70)	-
Inhaled corticosteroids + long-acting bronchodilators			-
No	N.A.	2 (10)	-
Salmeterol	N.A.	16 (80)	-
Formoterol	N.A.	2 (10)	-
Montelukast	N.A.	11 (55)	-
Omalizumab	N.A.	6 (30)	-

Data are presented as n (%) or mean (SD). N.A.: not available.

7.2 Distribution of HRCT findings

HRCT findings differentiated children with SA from controls across multiple airway- and parenchymal-level parameters. BT scores were consistently higher in the SA group across all lobes (right upper lobe, middle lobe, right lower lobe, left upper lobe, lingula, and left lower lobe), with controls exhibiting a BT score of 0.0 (0.0) in each lobe and SA showing mean BT scores ranging from 0.5 to 0.9; for each lobe, differences were statistically significant ($p \leq 0.001$). Airway wall thickness percentage (AWT%) was also significantly higher in SA compared with controls (43.9

[3.6] vs 34.8 [2.4], p < 0.001). In contrast, air trapping (AT) score was low in both groups and did not significantly differ (0.1 [0.5] vs 0.0 [0.0], p = 0.142), consistent with the absence of expiratory acquisitions for quantitative assessment. Bronchiectasis was present only in the SA group and was reflected by higher bronchiectasis grading (BG) and bronchiectasis severity (BS) scores (both p = 0.016). Mucus plugging and centrilobular emphysema were observed exclusively in SA (each 6/20, 30%), reaching statistical significance compared with controls (p = 0.009 for both). Qualitative findings such as ground-glass opacities, small centrilobular opacities, air space consolidation, and collapse were infrequent and did not significantly differ between groups. Airways volume and total lung volume were similar between groups (Table 3).

Table 3. Distribution of radiological findings by disease status.

	Controls n	Severe asthmatics n=	Univariate analysis p-value	Random Forest p-value	Adjusted R. Forest p-value
Bronchial thickening (BT) score, right upper lobe (RUL)	0.0 (0.0)	0.5 (0.7)	**0.001**	**<0.001**	**<0.001**
Bronchial thickening (BT) score, middle lobe (ML)	0.0 (0.0)	0.9 (0.7)	**<0.001**	**<0.001**	**<0.001**
Bronchial thickening (BT) score, right lower lobe (RLL)	0.0 (0.0)	0.9 (0.8)	**<0.001**	**<0.001**	**<0.001**
Bronchial thickening (BT) score, left upper lobe (LUL)	0.0 (0.0)	0.7 (0.7)	**<0.001**	**<0.001**	**<0.001**
Bronchial thickening (BT) score, lingula (L)	0.0 (0.0)	0.7 (0.7)	**<0.001**	**<0.001**	**<0.001**
Bronchial thickening (BT) score, left lower lobe (LLL)	0.0 (0.0)	0.9 (0.8)	**<0.001**	**<0.001**	**<0.001**
Air trapping (AT) score	0.0 (0.0)	0.1 (0.5)	0.142	0.500	1.000
Airway wall thickness percentage (AWT%)	34.8 (2.4)	43.9 (3.6)	**<0.001**	**<0.001**	**<0.001**
Inspiratory decreased lung attenuation (IDLA)	0 (0)	2 (10)	0.232	0.500	1.000
Small centrolobular opacities (SCO)	1 (5)	4 (20)	0.184	0.938	1.000
Broncho-arterial (BA) diameter ratio (B1)	1.0 (0.0)	1.0 (0.1)	0.192	0.613	1.000
Broncho-arterial (BA) diameter ratio (B10)	1.0 (0.1)	1.0 (0.1)	0.348	0.418	1.000
Bronchiectasis grading (BG) score	0.0 (0.0)	0.2 (0.4)	**0.016**	**0.003**	0.071
Bronchiectasis severity (BS) score	0.0 (0.0)	0.2 (0.4)	**0.016**	**0.022**	0.536
Ground glass (GG) opacities	2 (10)	4 (20)	0.410	0.700	1.000
Air space consolidation (ASC)	0 (0)	3 (15)	0.107	0.091	1.000
Mucus plugging (MP)	0 (0)	6 (30)	**0.009**	**0.006**	0.135
Collapse	0 (0)	3 (15)	0.107	0.500	1.000
Centrilobular emphysema	0 (0)	6 (30)	**0.009**	**<0.001**	**<0.001**
Panlobular emphysema	0 (0)	0 (0)	N.A.	0.500	1.000
Paraseptal emphysema	0 (0)	1 (5)	0.488	0.500	1.000
Irregular emphysema	0 (0)	0 (0)	N.A.	0.500	1.000
Airways volume	22.0 (11.8)	20.8 (14.6)	0.593	0.444	1.000
Lung volume	2706.0 (1205.4)	2666.8 (1426.8)	0.657	0.999	1.000

Data are presented as n (%) or mean (SD). N.A.: not available. Significant p-values are in bold.

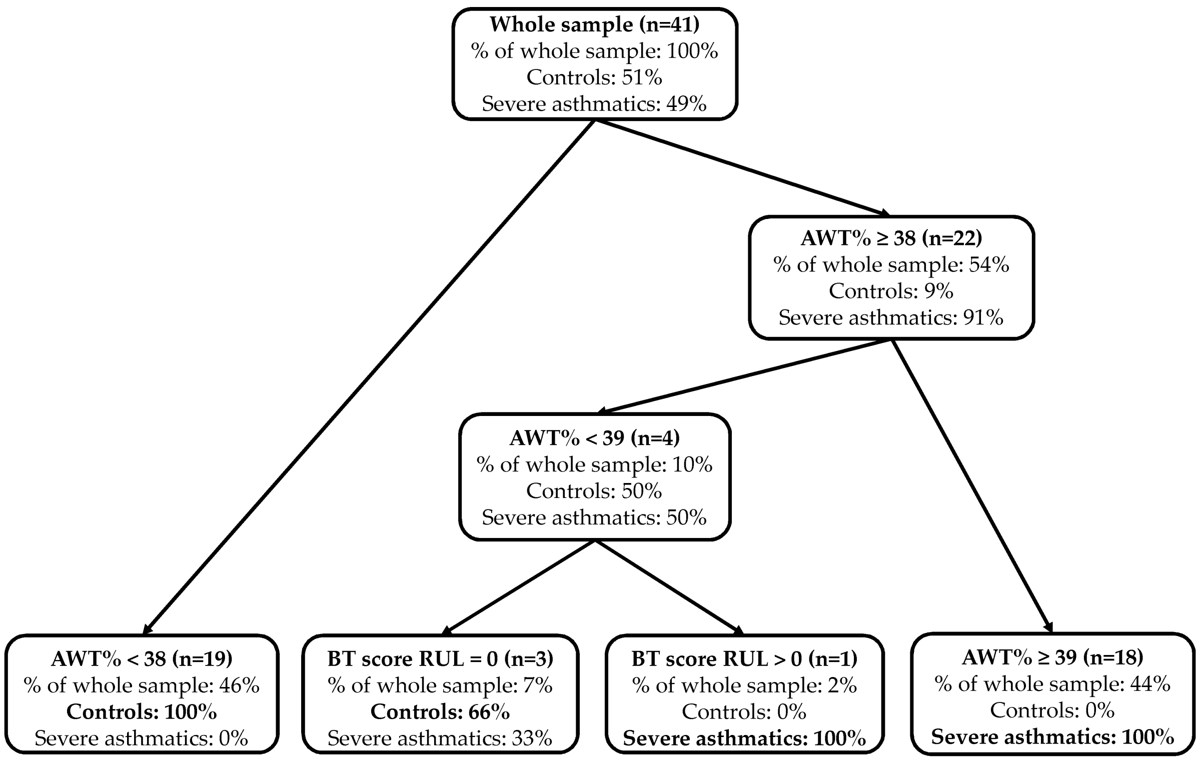
7.3 Machine learning classifiers and diagnostic performance

7.3.1 Classification tree

The classification tree yielding the best cross-validated accuracy consisted of four terminal nodes. AWT% < 38 identified a subgroup comprising 19 children, all controls. AWT% ≥ 39 identified a subgroup comprising 18 children, all severe asthmatics. Two intermediate groups were defined by AWT% between 38 (inclusive) and 39 (exclusive); within this range, a right upper lobe BT score equal to 0 classified a small subgroup (n = 3) predominantly controls, whereas BT score > 0 identified a subgroup containing a severe asthmatic child (n = 1) (Figure 1). Performance was high:

sensitivity 95%, specificity 100%, and accuracy 98% in the training set; cross-validated accuracy was 90% (LOOCV).

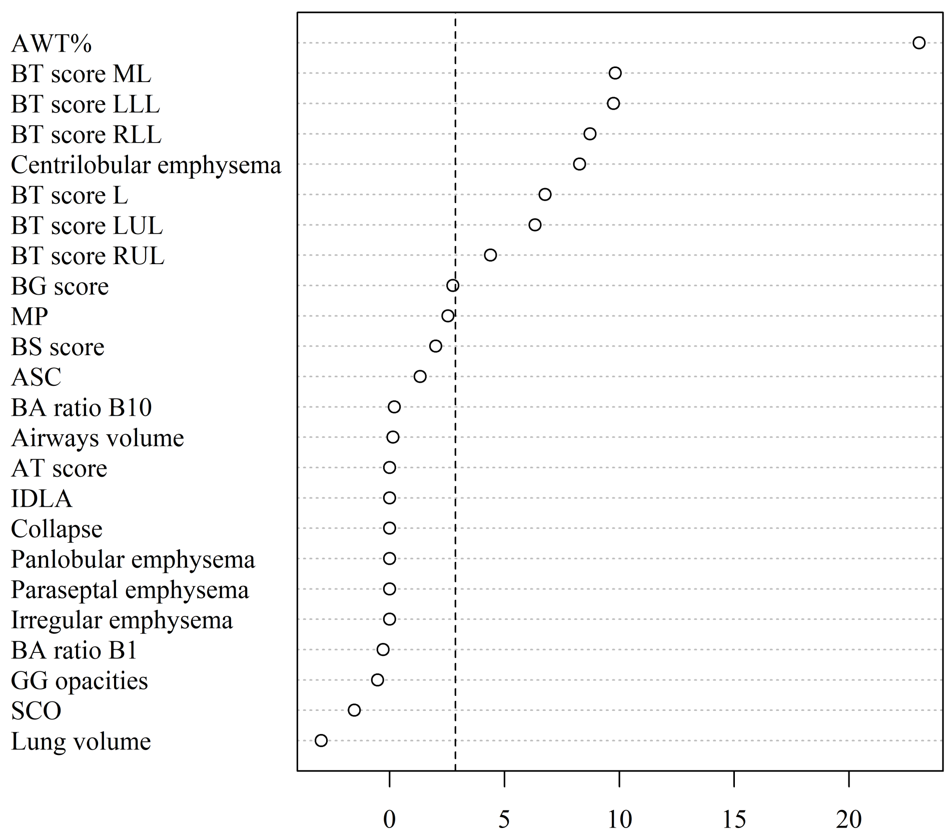
Figure 1. Best regression tree (according to the cross-validated accuracy) using the disease status as the outcome and radiological findings as the predictors. AWT%: airway wall thickness percentage RUL: Right upper lobe.



7.3.2 Random forest

The best-performing random forest model (selected by LOOCV) used M = 5 candidate predictors sampled at each split (Figure 2). AWT% had the highest normalized permutation importance, followed by BT scores and centrilobular emphysema; after Bonferroni adjustment, AWT% remained the only predictor retaining statistical significance for importance. The random forest achieved sensitivity 95%, specificity 100%, and accuracy 98% in both the training set and under LOOCV.

Figure 2. Normalized permutation importance of radiological findings for the prediction of the disease status using the best random forest (according to the cross-validated accuracy). Dashed line: minimum value associated with a significant adjusted p-value.



AWT%: airway wall thickness percentage; BT: Bronchial thickening; ML: Middle lobe; LLL: Left lower lobe; RLL: Right lower lobe; L: Lingula; LUL: Left upper lobe; RUL: Right upper lobe ; BG: Bronchiectasis grading; MP: Mucus plugging; BS: Bronchiectasis severity; ASC: Air space consolidation; BA: Bronchial-arterial; AT: Air trapping; IDLA: Inspiratory decreased lung attenuation; GG: Ground glass; SCO: Centrilobular opacities

7.3.3 ROC-based binary classifier

Conventional ROC analysis using AWT% as the single predictor identified an optimal cut-off of AWT% ≥ 38.6 (Figure 3). The resulting classifier achieved sensitivity, specificity, and overall accuracy of 95% in the training set and 90% under LOOCV (Table 4). The AUC was 0.99 with a 95% confidence interval of 0.98–1.00. Figure 3. Receiver operating characteristic (ROC) curve for the ability of AWT% to predict the disease status. The best cut-off (point closest to the top left corner) and the area under the ROC curve (AUC) are superimposed.

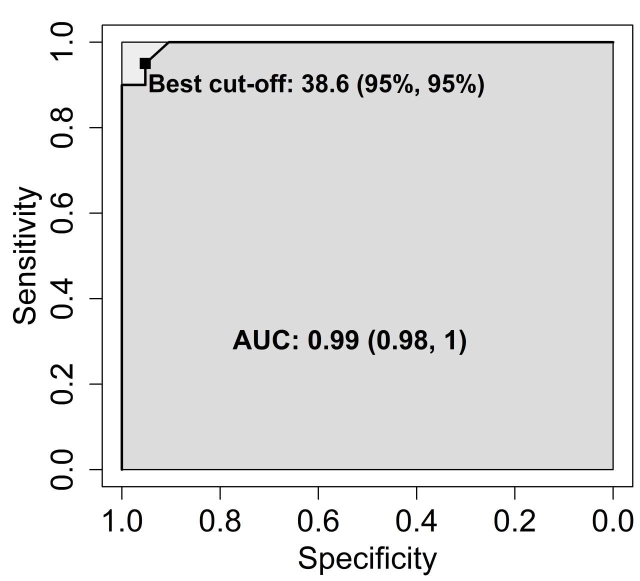


Table 4. Performance indicators of the different classifiers for disease status prediction.

	Classification tree		Random Forest		AWT% ≥ 38.6	
	Training set	Cross-validated	Training set	Cross-validated	Training set	Cross-validated
Sensitivity	95%	90%	95%	95%	95%	90%
Specificity	100%	90%	100%	100%	95%	90%
Accuracy	98%	90%	98%	98%	95%	90%

8. Discussion

8.1. Summary of principal findings

This thesis work supports the concept that chest HRCT, when interpreted through a combined qualitative–quantitative framework, can provide clinically meaningful information in pediatric severe asthma that complements conventional functional and inflammatory assessments. In a retrospective case–control design (20 children with severe asthma vs 21 age- and sex-matched controls), several structural abnormalities were significantly more prevalent (or exclusively present) in severe asthma, including higher BT scores, increased AWT%, higher bronchiectasis grading/severity scores, mucus plugging, and centrilobular emphysema. Among all evaluated imaging variables, AWT% emerged as the most discriminative feature. A conventional ROC approach identified an AWT% threshold of ≥38.6 as the best binary classifier for severe asthma versus controls, with high sensitivity/specificity and an "outstanding" AUC (0.99). Consistently, ML classifiers (classification tree and random forest) ranked AWT% as the dominant predictor, with BT scores contributing to the refinement of borderline cases. Collectively, these findings suggest that (i) measurable airway remodeling is detectable in children with severe asthma, (ii) selected HRCT features can separate severe asthma from non-asthmatic controls with high accuracy in this dataset, and (iii) quantitative/AI-enabled interpretation may reduce the subjectivity that limited earlier pediatric HRCT scoring approaches.

8.2. Airway wall thickening as an imaging surrogate of remodeling

Airway remodeling is a core pathobiological feature of severe asthma, yet direct assessment in children is constrained by the invasiveness of bronchoscopic sampling. The present results, showing higher BT scores and markedly increased AWT% in severe asthma, fit well within a broader body of quantitative CT evidence linking airway wall thickening with disease severity and airflow limitation. In adults, multidetector CT (MDCT) studies have demonstrated that wall-based metrics (e.g., WA%, WT%) are higher in severe asthma than in mild-to-moderate asthma and in healthy comparators, correlate inversely with baseline FEV_1, and correlate with pathologic measures of remodeling (including epithelial thickness on biopsy). These observations provide biologic plausibility to interpret increased AWT% in pediatric severe asthma as a noninvasive marker that is directionally consistent with remodeling-related airway wall expansion and lumen compromise. Pediatric data remain comparatively limited but are increasingly supportive. Quantitative CT work in children with severe asthma has reported higher AWT/AWT% than in controls and strong negative correlations between AWT% and spirometric indices (including FVC and FEV_1), with higher AWT% observed in previously hospitalized children. The convergence between these pediatric correlations and the adult pathology-linked findings reinforces the rationale to treat AWT% not merely as a radiologic descriptor, but as a candidate imaging biomarker with potential functional and prognostic implications—provided that technical variability is appropriately managed.

8.3. Small-airway dysfunction and air trapping: interpretation and methodological considerations

Small-airway involvement is a major driver of fixed obstruction, hyperinflation, and symptom burden, and CT-derived air trapping indices are frequently used as structural–functional proxies of distal airway disease. Quantitative CT phenotyping studies in uncontrolled/severe asthma have emphasized that air trapping indices can be sensitive markers of small-airway obstruction and may correlate with clinically meaningful variables (e.g., lung function, atopy/IgE, and corticosteroid exposure). However, air trapping is also the domain in which technical factors exert a large influence. Reliable quantification depends on (i) standardized inspiratory and expiratory acquisition, (ii) appropriate coaching and quality control of breath-holds, and (iii) harmonized reconstruction parameters and thresholds. The methodological descriptions of quantitative CT phenotyping studies underscore routine use of both full-inspiration and end-expiration acquisitions, daily scanner calibration, and patient training for breath-holds, procedural steps that are particularly critical in children. The pediatric HRCT literature also illustrates that qualitative scoring alone can obscure associations with physiology. In earlier pediatric cohorts with difficult-to-treat asthma, expiratory air trapping was common, whereas correlations between semi-quantitative bronchial wall thickening scores and spirometric measures were not consistently observed; subjectivity and limited reproducibility of wall-thickness scoring were explicitly highlighted as constraints. These observations contextualize why the present work's strongest signal was captured by a quantitative airway metric (AWT%) rather than by semi-quantitative air trapping scores, and why future pediatric studies should preferentially integrate standardized quantitative air trapping indices when feasible. Finally, imaging-biomarker frameworks in asthma emphasize that air-trapping phenotypes identified on CT can map onto more severe clinical profiles, including greater healthcare utilization and greater airflow limitation, supporting the clinical relevance of robust air trapping quantification beyond descriptive radiology.

8.4. Bronchiectasis as a comorbidity and potential consequence of severe pediatric asthma

Bronchiectasis is a key "rule-out/rule-in" target for HRCT in children with severe asthma, reflecting both the need to exclude alternative diagnoses and the possibility that chronic inflammation, mucus retention, and recurrent infection may contribute to structural airway dilation over time. In the present dataset, bronchiectasis grading and severity scores were higher in severe asthma than in controls. From a clinical perspective, the value of identifying bronchiectasis in severe pediatric asthma extends beyond labeling: it can prompt structured evaluation of infection risk, airway clearance strategies, microbiologic surveillance where appropriate, and reconsideration of overlapping or mimicking conditions. Even when bronchiectasis is mild, its detection may reframe "severe asthma" as a complex airway disease with treatable traits requiring multidimensional management rather than stepwise escalation of anti-inflammatory therapy alone. At the same time, caution is warranted in interpreting prevalence and severity across studies because detection is sensitive to acquisition protocols, expiratory vs inspiratory emphasis, airway generation analyzed, and the degree of automation applied. The present work, and the broader pediatric literature, therefore supports an approach where bronchiectasis on HRCT is interpreted within a protocol-aware framework and integrated with clinical trajectory, microbiology, and functional impairment rather than treated as a standalone determinant.

8.5. Mucus plugging and the concept of imaging-defined treatable traits

Mucus plugging contributes to airflow obstruction, ventilation heterogeneity, and exacerbation risk, and it has gained prominence as an imaging-visible trait in severe asthma. In the present dataset, mucus plugging was observed in a substantial subset of children with severe asthma and was absent in controls, reinforcing its potential role as a differentiating feature in severe disease. The implication for pediatric severe asthma is twofold. First, mucus plugging can help explain discordance between symptom burden/exacerbations and spirometric severity, given the patchy and regionally heterogeneous nature of plugging. Second, it points toward an actionable axis of care: optimizing inhaled therapy technique and adherence, addressing type-2 inflammation where present, evaluating comorbidities that increase mucus burden, and considering airway clearance strategies in selected cases. While definitive pediatric outcome data remain limited, the directionality of evidence supports inclusion of mucus plugging among the candidate HRCT features that may inform phenotyping and longitudinal risk stratification, particularly when paired with quantitative airway metrics.

8.6. Centrilobular emphysema and parenchymal abnormalities in children: signal, interpretation, and uncertainty

A notable observation in this cohort was the presence of centrilobular emphysema in a subset of children with severe asthma, while emphysema was absent in controls. Although emphysema is classically associated with smoking-related COPD, adult asthma imaging literature recognizes that emphysema-like low attenuation can coexist with severe asthma in specific contexts and may relate to long-standing disease, airway inflammation, and remodeling trajectories. In pediatrics, this finding should be treated as hypothesis-generating rather than definitive. Potential explanations include true parenchymal destruction in a severe endotype, regional overdistension misclassified as emphysema-like change, or technical influences related to lung volume at acquisition. The critical next step is longitudinal validation with standardized low-dose protocols and, where possible, complementary functional imaging (e.g., MRI ventilation approaches) to determine whether these parenchymal patterns persist, progress, or respond to improved disease control.

8.7. Added value of machine learning and quantitative HRCT in pediatric severe asthma

A core contribution of this thesis work is the demonstration that ML methods applied to HRCT-derived features can yield high diagnostic discrimination between pediatric severe asthma and controls, while simultaneously identifying a compact set of dominant predictors (chiefly AWT%). This is clinically relevant because it reframes HRCT from a purely exclusionary test (to rule out comorbidities) into a potential decision-support input that captures structural disease burden and heterogeneity. Several aspects are important when translating these findings into future practice or research:

- Interpretability and parsimony: The strong performance achieved by AWT% alone (including the ≥38.6 threshold) suggests that the model's signal is not dependent on opaque high-dimensional features; it is driven by a clinically intelligible marker of airway wall remodeling.
- Complementarity between quantitative and semi-quantitative metrics: Classification tree logic indicated that BT scores refined classification in intermediate AWT% ranges, consistent with a framework where multiple airway features provide additive discrimination across severity gradients.
- Reproducibility constraints: Variability in reported AWT% values across pediatric studies has been attributed to differences in software applications, analytic pipelines, and cohort characteristics.

This reinforces that pediatric-specific normative ranges and cross-platform harmonization are prerequisites before fixed thresholds can be generalized beyond single-center cohorts. In aggregate, these results support a pragmatic translational pathway: (i) standardize acquisition and quantitative extraction, (ii) validate a small set of robust metrics (e.g., AWT%, validated air trapping indices), and (iii) integrate those metrics into multivariable clinical models that include biomarkers, exacerbation history, and treatment exposure.

8.8. Limitations

Several limitations should guide interpretation:

- Retrospective design and sample size: The cohort size is modest, and model performance estimates may be optimistic in small datasets despite cross-validation.
- Case–control structure: Controls were selected as non-asthmatic comparators; this design optimizes discrimination but does not directly address differentiation among asthma severities or among uncontrolled asthma phenotypes.
- Selection and indication bias: HRCT in children is typically performed for specific clinical indications; therefore, structural findings may over-represent more complex or atypical cases within the severe asthma spectrum.
- Measurement variability: Quantitative airway measures depend on segmentation quality, breath-hold level, reconstruction parameters, and analytic software. Between-study variability in AWT% underscores the need for harmonization and pediatric reference standards.
- Limited longitudinal linkage: Although the study identifies discriminative structural features, definitive claims about prediction of long-term outcomes in children require prospective follow-up. 1. Adult longitudinal CT work suggests that airway wall metrics can change over time and relate to lung-function decline, but pediatric confirmation is needed.

8.9. Future directions

Based on the current findings and the trajectory of quantitative asthma imaging research, several priorities emerge:

- Prospective, multicenter pediatric validation with harmonized acquisition (inspiratory/expiratory coaching, calibration, standardized reconstruction) and pre-specified quantitative endpoints.
- Development of pediatric normative datasets for airway dimensions and wall metrics across age, sex, and body size to enable robust z-scoring and improve comparability between platforms.
- Outcome-linked modeling, testing whether baseline AWT% (and validated air trapping indices) predict exacerbation burden, hospitalization, treatment response to biologics, and lung-function trajectories—an approach supported by adult evidence that quantitative CT metrics relate to airflow obstruction and remodeling biology.
- Integrated phenotyping, combining imaging metrics with inflammatory biomarkers and clinical treatable traits to refine stratification beyond “severe vs non-severe,” aligning imaging with precision medicine frameworks.
- Radiation-aware longitudinal strategies, including strict ALARA application, selective scanning, and, where feasible, complementary non-ionizing approaches for follow-up in children, reserving HRCT for high-yield clinical questions and validated research protocols.

9. Conclusions

This doctoral work supports the concept that HRCT, when interpreted through a structured qualitative–quantitative framework, can provide objective markers of severe pediatric asthma that complement conventional clinical and functional assessment. In this retrospective case–control cohort, children with severe asthma exhibited a distinctive structural signature on HRCT, characterized by increased airway wall abnormalities (higher BT scores and markedly increased AWT%), and by the presence of additional management-relevant findings such as bronchiectasis, mucus plugging, and centrilobular emphysema. Across analytical strategies, AWT% emerged as the most informative imaging feature, enabling discrimination between severe asthma and non-asthmatic controls with high accuracy and yielding an optimal cut-off (AWT% $\geq$ 38.6) with excellent diagnostic performance under internal validation. These findings are consistent with the current literature indicating that airway remodeling is already detectable in childhood severe asthma and that quantitative imaging metrics can reduce observer dependence and operationalize structural disease into candidate biomarkers. From a translational perspective, this work provides a methodological and clinical rationale for incorporating quantitative HRCT-derived indices into pediatric severe asthma phenotyping, particularly in carefully selected patients undergoing imaging for appropriate indications. At the same time, the results should be interpreted in light of the study's retrospective design, limited sample size, and the need for protocol harmonization and external validation across scanners, software platforms, and populations. Future multicenter prospective studies are warranted to validate AWT%-based thresholds, integrate expiratory imaging for robust assessment of small-airway disease, and determine whether baseline HRCT biomarkers predict clinically meaningful longitudinal outcomes such as exacerbation risk, treatment response, and lung function trajectories. Such efforts should proceed within strict radiation stewardship principles and, where feasible, in conjunction with non-ionizing functional imaging modalities.

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Appendix

Lung function assessment

Spirometry was conducted according to ATS/ERS guidelines using a calibrated spirometer, and the best of three technically acceptable maneuvers was recorded.

Bronchodilator responsiveness (BDR) was calculated as the percent change in FEV1 after administration of a short-acting bronchodilator (salbutamol 400 mcg), with a positive response defined as an increase of ≥12% and ≥200 mL in FEV1.

HRCT Protocol:

Scans were acquired in the cranio-caudal direction using helical acquisition and without contrast medium administration. Key parameters were:

- Tube voltage: 100-120 kV
- Tube current: 50-60 mAs
- Collimation: 0.75 mm
- Reconstruction slice thickness: 1 mm
- Reconstruction interval: 1 mm
- Matrix: 512 x 512
- High-spatial frequency algorithm for optimized spatial resolution
- Parenchymal window (width: 1800 HU, level: -600 HU)
- Patient-adjusted field of view (FOV): 15-35 cm

CT Image Analysis for Airway Assessment:

The COPD application provides semiautomatic and manual tools to facilitate the visualization and measurement of pulmonary findings in children with severe asthma.

Key features include:

- Lung Volume Calculation: The software calculates lung volume from CT images, enabling the normalization of airway measurements.
- Thin Section Reconstruction: The application reconstructs thin CT sections orthogonal to the central axis of visible bronchi, optimized for detailed airway measurements.
- Airway Measurements:

  The following parameters are measured:

  - Cross-sectional bronchial lumen area (BLA)
  - Wall area (WA)
  - Airway wall thickening (AWT)
  - Average lumen diameter (LB)
  - Lumen max diameter
  - Ratio of wall area to lumen area (WA/LA)
  - Airway max diameter

- Average airway diameter
- Airway effective diameter
- Airway area (AA)

- Bronchial Generation Assessment: The software aids in determining the bronchial generation, which is a factor in certain measurements.

Bronchial Analysis

All visible bronchi were analyzed using the Weibel model.[1,2] The trachea was designated generation 0, with the generation incrementing after each successive bifurcation. For normalization purposes, measurements were adjusted by body mass index (BMI) and body surface area (BSA).

Additional CT Imaging Characteristics

The following were also assessed:

- Bronchial-arterial ratio (BA ratio): Calculated from basal scans by dividing the average diameter of the bronchial lumen (at right B1 and right B10) by the average diameter of the accompanying artery (measured at the segmental to sub-segmental level). Ratios exceeding 1.5 or below 0.65 were considered pathological.[14-19]
- Bronchiectasis (BE): Graded for severity and classified by type (I: cylindrical, II: varicose, III: cystic).
- Emphysema: Quantified using analysis software and qualitatively classified (centrilobular, pan-lobular, paraseptal, or irregular).

Bronchial Thickening Quantification

- Bronchial Thickening Score (BT Score): This semi-quantitative score assessed thickening in identifiable third (segmental) and fourth (sub-segmental) generation bronchi. A separate score was assigned to each pulmonary lobe (including the lingula) (E-Table 1).
- Airway Wall Thickness (AWT): Visible segmental and sub-segmental airway/vessel pairs with a rounded cross-section were manually measured using electronic calipers to determine outer (Do) and inner (Di) diameters. The percentage of airway wall thickness (AWT%) was calculated as follows: AWT% = [(Do-Di)/Do] x 100.

Mucus Plugging and Other Opacities

- Mucus plugging (MP): Identified as segmental densities larger than adjacent pulmonary arteries, appearing in characteristic shapes (beaded, gloved finger-like, nodular, or oval) across consecutive scans.

Qualitative analysis included assessment for: Small centrilobular opacities (SCO), ground-glass opacities (GG), air space consolidation (ASC), and collapse.

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