ORIGINAL ARTICLE

# Severe Asthma Phenotypes Classified by Site of Airway Involvement and Remodeling via Chest CT Scan

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## Abstract

*Objectives:* This study aimed to establish a system that can classify severe asthma on the basis of airway remodeling patterns visualized using computed tomography (CT) images and to evaluate the clinical characteristics of individual image-based subtypes.
*Methods:* Chest CT images from severe asthma patients were retrospectively evaluated to classify phenotypes by site of airway involvement and remodeling. The association between radiologic subtypes and clinical characteristics was assessed.
*Results:* Of 91 patients with severe asthma, 74 (81.3%) exhibited abnormal radiologic findings, including bronchial wall thickening (BT), mucus plugging (MP), and bronchiectasis (BE). The severity of BT and the extent of MP were independently associated with peripheral blood eosinophil count ($P$=.012, $r^2$=0.112) and sputum eosinophil count ($P$=.022, $r^2$=0.090), respectively. The large-to-medium airway remodeling type, which showed diffuse BT combined with MP and BE, accounted for 44% of patients and revealed higher peripheral blood eosinophil counts than other types. In the small airway remodeling type, which accounted for 6.6% of patients, we observed a higher rate of fixed airflow obstruction, along with a predominance of males and smokers and more frequent use of controller medication than other phenotypes. In 26% of patients with severe asthma, no prominent airway remodeling was observed (near-normal type); the near-normal type required oral corticosteroids less frequently than the large-to-medium airway and small airway remodeling types.
*Conclusions:* Depending on the site of airway involvement and remodeling pattern, 3 different structural types can be distinguished in chest CT findings from patients with severe asthma. Remodeling in large-to-medium sized airways revealed an association with systemic eosinophilic inflammation in patients with severe asthma.

Key words: Asthma. Phenotype. Tomography. X-ray. Airway remodeling.

## Resumen

*Objetivos:* Este estudio tuvo como objetivo establecer un sistema que pueda clasificar el asma grave en función de los patrones de remodelación de la vía aérea visualizados mediante imágenes de tomografía computarizada (TC) y para evaluar las características clínicas de los subtipos de pacientes basados en imágenes.
*Métodos:* Las imágenes de tomografía computarizada del tórax de pacientes con asma grave se evaluaron retrospectivamente para clasificar fenotipos por sitio de afectación y remodelación de la vía aérea. También se evaluó la asociación entre los subtipos radiológicos y las características clínicas.
*Resultados:* De 91 pacientes con asma severa, 74 (81,3%) exhibieron hallazgos radiológicos anormales, incluyendo engrosamiento de la pared bronquial (BT), taponamiento de moco (MP) o bronquiectasias (BE). La gravedad del BT y la puntuación de extensión de MP se asociaron de forma independiente con el recuento de eosinófilos en sangre periférica (p= 0,012, $r^2$= 0,112) y el recuento de eosinófilos en esputo (p= 0,022, $r^2$= 0,090), respectivamente. El tipo de remodelación de la vía respiratoria grande a mediana (tipo LA), que muestra una BT difusa combinada con MP y BE, representó el 44% del total de pacientes y presentó recuentos de eosinófilos en sangre periférica más altos que otros tipos. El tipo de remodelación de la vía aérea pequeña (tipo SA), que constituyó el 6,6% de los pacientes, mostró una mayor tasa de obstrucción del flujo de aire fijo, junto con el predominio de hombres y fumadores y un mayor uso de medicación controladora que otros fenotipos. En el 26% de los pacientes con asma grave, no se observó una remodelación prominente de la vía aérea (tipo casi normal, tipo NN). El tipo NN mostró menos requerimientos de esteroides orales en relación con los tipos LA y SA.

*Conclusiones:* Se pueden distinguir tres tipos estructurales diferentes mediante los hallazgos de la TC de tórax, según el sitio de afectación de la vía aérea y el patrón de remodelación en los pulmones de pacientes con asma grave. La remodelación de las vías respiratorias de grandes a medianas reveló una asociación con la inflamación eosinofílica sistémica en el asma grave.

**Palabras clave:** Asma. Fenotipo. Tomografía. Rayos X. Remodelación de las vías respiratorias.

## Introduction

Asthma is a common inflammatory airway disorder whose prevalence is increasing worldwide. Approximately 5%-10% of asthma patients exhibit a severe form that is resistant to conventional treatment [1,2] and thus generates a substantial economic burden. Therefore, the study of severe asthma is an important and challenging area of research because of the need to understand its mechanisms, reduce related morbidity and healthcare costs, and develop effective treatments. Emerging data from numerous studies suggest that severe asthma is a syndrome of heterogeneous conditions, and various researchers recently attempted to classify phenotypes of severe asthma using clinically observable characteristics in a large-scale cohort [3-7].

Computed tomography (CT) is an ideal noninvasive modality for assessment of the distribution, extent, and severity of morphological changes in the airways and lung parenchyma. Although CT is not an essential diagnostic test for asthmatic patients, it helps to identify comorbid conditions, such as allergic bronchopulmonary aspergillosis and Churg-Strauss syndrome, and to detect diseases that mimic asthma. In a large cohort study, approximately 80% of patients with severe asthma showed abnormalities in their chest CT images, thus suggesting a potential role for CT in evaluating severe asthma [8]. In addition, advances in current imaging techniques have enabled the differentiation of severe asthma by quantitative assessments, thereby providing new opportunities to understand severe asthma [9,10]. However, clinical subtypes of severe asthma based on the structural characteristics of the airways and lung parenchyma have not yet been firmly established.

We hypothesized that the site of airway involvement and remodeling visible on CT scans could be used to determine phenotypes of asthma. Therefore, the objectives of this study were to investigate the association between clinical characteristics and CT parameters in patients with severe asthma and to suggest a classification system for severe asthma based on airway remodeling patterns visible in CT images.

## Materials and Methods

### *Study Patients*

A retrospective study was conducted based on data from patients with severe asthma who were followed up at an allergy clinic in a tertiary care hospital for at least 1 year and who underwent CT scans between September 2002 and July 2013. A detailed review of the medical records of all patients was performed, including baseline demographics, skin prick tests for common aeroallergens, pulmonary function tests, peripheral blood and induced sputum test results, and prescriptions for asthma.

Diagnosis of asthma was confirmed by 2 allergy specialists based on the patient's medical history and the presence of at least 1 of the following criteria: (*1*) bronchodilator reversibility, characterized by an increase in the forced expiratory volume in 1 second ($FEV_1$) that was >12% and >200 mL from baseline following inhalation of 400 μg of salbutamol; (*2*) a positive response to a methacholine inhalation challenge, which was defined as provocative concentration causing a 20% drop in $FEV_1$ ($PC_{20}$) of <16 mg/mL. Severe asthma patients were defined as having asthma that requires treatment with high-dose inhaled corticosteroids (dose equivalent to ≥1000 μg of beclomethasone), along with a second controller treatment to prevent the asthma from becoming uncontrolled, or as having asthma that remains uncontrolled despite this treatment [11]. Patients were excluded if they had not received appropriate antiasthmatic treatment for at least 1 year before undergoing the CT scan. Institutional Review Board approval was obtained; the need for written informed consent was waived.

### *Image Evaluation*

Imaging was performed using a 64-slice multidetector CT scanner (Ingenuity, Philips Healthcare) under full inspiration and full expiration. The CT parameters were as follows: reference mAs of 200, 120 kVp, 1.0 mm reconstruction thickness, 1.0 mm reconstruction increment, YC0 reconstruction filter, and 0.5 sec rotation time. All CT scans were evaluated by 2 thoracic radiologists (15 years and 10 years of experience) who were blinded to each patient's clinical information; both radiologists reached a consensus on each evaluation. Bronchial wall thickening, mucus plugging, bronchiectasis, and lung parenchymal changes were analyzed. The extent of bronchial wall thickening, mucus plugging, and bronchiectasis was evaluated as the number of involved lobes (range, 0-5). The severity of these parameters was assessed on a 4-point scale, ranging from 0 to 3 (0, no abnormality; 1, partial noncontinuous bronchial wall thickening and bronchiectasis/bronchial obstruction with mucus; 2, diffuse continuous bronchial wall thickening/mucus plugging/bronchiectasis; 3, diffuse continuous lesions that extended to the subpleural area). The air trapping index and emphysema index were defined, respectively, as the percentage of voxels <–856 HUexp and <–950 HUinsp on CT images. Classification of the main types of airway remodeling was as follows: (*1*) if the tracheal, lobar, segmental, or subsegmental bronchi were involved, then the classification was large or medium airway remodeling type

(large airway involvement, LA type); (*2*) if airways distal to the subsegmental bronchi were involved, or if air trapping or an emphysematous change was seen in the lung parenchyma, then the classification was small airway remodeling type (small airway involvement, SA type); and (*3*) if no remarkable abnormalities were observed, then the classification was near-normal type (normal or near-normal, NN type). Combinations of LA type and SA type were classified as either predominantly LA type or predominantly SA type, according to the Fleischner Society Statement (predominant LA type, <6% of pixels that are <–950 HU by quantitative CT; predominant SA type, >6% of pixels that are <–950 HU by quantitative CT, and/or visual identification of emphysema or air trappings) [12]. Both thoracic radiologists agreed on each classification after considering the extent to which the lobes were involved.

### *Statistical Analysis*

Continuous variables were summarized as median (IQR) or mean (SD). Percentile distributions were used to describe categorical variables. The association between clinical features and CT findings was evaluated by correlation and linear regression analysis. Age, sex, and variables for which $P<.1$ in the simple linear regression model were adjusted in the multiple linear regression analysis. To compare the continuous variables comprising clinical characteristics and CT indices, we performed an analysis of variance or Kruskal-Wallis test, depending on whether or not the variables were normally distributed. The Fisher exact test was used to compare categorical variables. Differences were considered significant if the $P$ value was <.05. If the Kruskal-Wallis test resulted in a $P$ value <.05, pairwise comparisons of subgroups were performed using MedCalc version 13, in accordance with the Conover method [13]. Post hoc analysis between subgroups was performed for significant categorical variables using the Fisher exact test, in which a $P$ value of .017 was considered to indicate statistical significance (following a Bonferroni correction). All statistical analyses, except pairwise comparisons after the Kruskal-Wallis test, were performed with SPSS version 23 (IBM Corp).

## Results

### *Characteristic Clinical and CT-Based Findings for Severe Asthma Patients*

Of a total of 91 severe asthma patients who satisfied the inclusion criteria during the study period, bronchial wall thickening was observed in 60 patients (65.9%), mucus plugging in 57 patients (62.6%), and bronchiectasis in 32 patients (35.2%). Seventy-four patients (81.3%) exhibited at least 1 of these findings. The mean (SD) emphysema index was 12.6% (12.9%), whereas the mean air trapping index was 29.9% (26.3%).

We evaluated the correlation between clinical features and CT parameters, such as the extent and severity of bronchial wall thickening, mucus plugging, and bronchiectasis, as well as the emphysema index and air trapping index. Although the severity of bronchial wall thickening was significantly correlated with peripheral blood eosinophil count ($P$=.042, r=0.216), it was not associated with sputum eosinophil count ($P$=.981, r=–0.003). There was an inverse correlation between severity of bronchial wall thickening and sputum neutrophil count ($P$=.048, r=–0.261). The extent of bronchial wall thickening was not significantly associated with clinical parameters. Although there were no significant correlations between severity of mucus plugging and other clinical characteristics, the extent of mucus plugging correlated positively with sputum eosinophil percentage ($P$=.027, r=0.288).

A greater extent of bronchiectasis was associated with a lower $FEV_1$ (% predicted) ($P$=.039, r=–0.217), and bronchiectasis was more severe in nonsmokers ($P$=.02, r=–0.287). The severity and the extent of bronchiectasis were significantly higher in female patients ($P$=.007, r=0.324; $P$=.046, r=0.210).

The emphysema index was positively correlated with age ($P$=.032, r=0.260), history of smoking ($P$=.004, r = 0.354), male sex ($P$=.017, r=0.290), and sputum neutrophilia ($P$=.020, r=0.341), whereas it was negatively correlated with $FEV_1$ (% predicted) ($P$=.005, r=–0.338), $FEV_1$/FVC (%) (P<.001, r=–0.490), and blood eosinophil count ($P$=.049, r=–0.243).

Table 1. Results of Multiple Linear Regression Analysis of Clinical Indices and Computed Tomography Findings[a]

| Dependent Variable | Independent Variable | Coefficient ($\beta$) | SE | $P$ Value | $R^2$ |
|---|---|---|---|---|---|
| BT severity score | PB eosinophil, cells/μL | 0.001 | 0.0002 | .012 | 0.112 |
| MP extent score | Sputum eosinophil, % | 0.030 | 0.013 | .022 | 0.090 |
| BE extent score | Sex: male (ref) vs female | 0.953 | 0.320 | .004 | 0.137 |
| | $FEV_1$, % predicted | –0.023 | 0.008 | .004 | |
| BE severity score | Sex: male (ref) vs female | 0.726 | 0.272 | .010 | 0.103 |
| Emphysema index, % | Smoker: never (ref) vs current or previous | 7.845 | 3.303 | .023 | 0.426 |
| | $FEV_1$/FVC, % | –0.375 | 0.113 | .002 | |

Abbreviations: BE, bronchiectasis; BT, bronchial wall thickening; $FEV_1$, first second of forced expiratory volume; FVC, forced vital capacity; MP, mucus plugging; PB, peripheral blood; ref, reference group; SE, standard error.
[a]Age, sex, and variables for which $P<.1$ in simple linear regression models were adjusted in the multiple linear regression analysis.

However, there were no meaningful correlations between the air trapping index and any of the clinical parameters included in this study.

The results of the multiple linear regression analysis of clinical indices and CT-based findings (airway conditions, emphysema index, and air trapping index) are shown in Table 1. After adjustment for various clinical variables (age, sex, and variables for which the *P* values were <.10 in simple linear regression models), the severity of bronchial wall thickening remained independently associated with peripheral blood eosinophil count ($P$=.012, $r^2$=0.112). The extent of mucus plugging was still significantly associated with sputum eosinophil count (%) ($P$=.022, $r^2$=0.090). The extent of bronchiectasis was higher in female patients and in patients with lower $FEV_1$ ($P$=.004 in both, $r^2$=0.137), but bronchiectasis severity scores were significantly higher only in female patients ($P$=.010, $r^2$=0.103). The emphysema index was significantly associated with smoking and low $FEV_1$/FVC (%) after adjustment ($P$=.023 for smoking; $P$=.002 for $FEV_1$/FVC, $r^2$=0.426); however, the air trapping index was not associated with any clinical parameters.

### *Clinical Features of Each Phenotype Based on Airway Remodeling Patterns*

Patterns in the airways and lung parenchyma of patients with severe asthma were classified into 3 distinctive categories based on the consensus of 2 radiologists: LA, SA, and NN types (Figure 1). The traits of the LA type included diffuse bronchial wall thickening combined with mucus plugging and bronchiectasis, whereas those of the SA type included prominently low attenuation in the CT image of the lung, but no evidence of mucus plugging. Although patients with the NN type demonstrated clinical manifestations of severe asthma, their airways were almost normal without marked airway remodeling. Some CT images revealed mixed patterns of LA and SA types, which were then subdivided according to their dominant pattern into a mixed type with a dominant pattern of large or medium airway remodeling (mLA) or a mixed type with a dominant pattern of small airway remodeling (mSA).

Among the 91 patients in this study, 70 were categorized into 1 of the 3 phenotypes; the LA type was the most common (40 patients, 44.0%), NN was the second-most

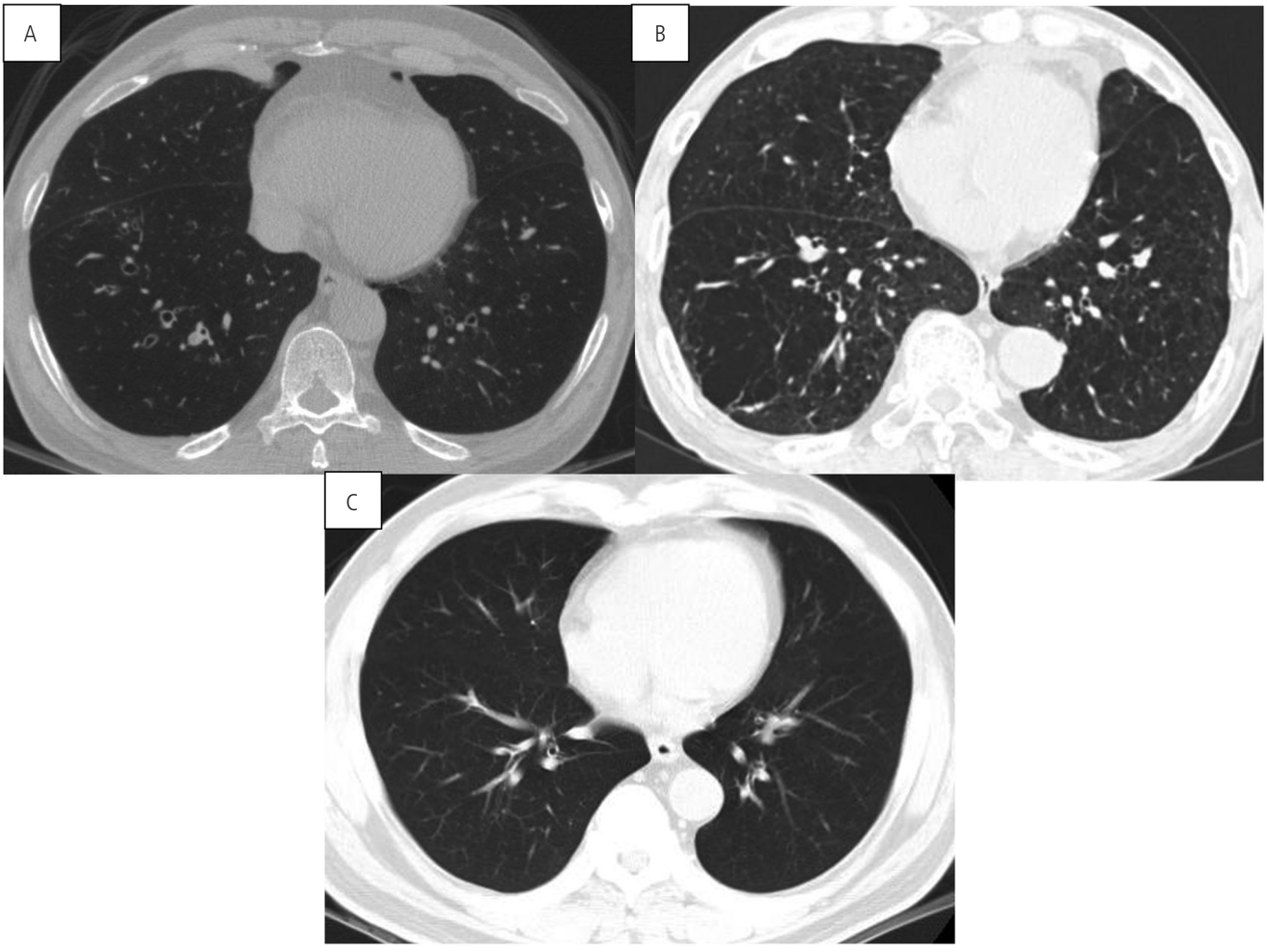


**Figure 1.** Representative computed tomography images of each phenotype. A, Large or medium airway remodeling. B, Small airway remodeling. C, Near-normal.

Table 2. Comparison of Clinical Characteristics for Individual Phenotypes[a]

| | LA type (n=40) | SA type (n=6) | NN type (n=24) | *P* Value |
|---|---|---|---|---|
| Onset age, y | 44.0 (40.0-51.0) | 49.5 (32.0-65.0) | 48.0 (39.0-56.5) | .640 |
| Age at which CT was performed, y | 58.0 (54.0-65.5) | 69.0 (68.0-72.0) | 61.0 (54.0-65.5) | .070 |
| Disease duration, y | 16.0 (12.0-21.0) | 26.0 (16.0-34.0) | 12.5 (8.0-20.0) | .078 |
| BMI, kg/m$^2$ | 24.3 (3.8) | 20.8 (3.7) | 24.0 (2.7) | .656 |
| Sex, No. (%) | | | | .003 |
| Male | 13 (32.5%)[a] | 6 (100.0%)[a] | 14 (58.3%) | |
| Female | 27 (67.5%)[a] | 0 (0.0%)[a] | 10 (41.7%) | |
| Smoking status, No. (%) | | | | .003 |
| Never smoked | 29 (72.5%)[a] | 0 (0.0%)[a,b] | 15 (62.5%)[b] | |
| Ex- or current smoker | 11 (27.5%)[a] | 6 (100.0%)[a,b] | 9 (37.5%)b | |
| Atopy, No. (%) | 20 (52.6%) | 2 (33.3%) | 11 (47.8%) | .670 |
| Sinusitis, No. (%) | 29 (72.5%) | 1 (20.0%) | 14 (60.9%) | .061 |
| Aspirin intolerance, No. (%) | 2 (5.0%) | 0 (0.0%) | 3 (12.5%) | .411 |
| Sputum eosinophil, % | 16.2 (5.3-25.7) | 7.8 (3.0-12.0) | 6.7 (3.2-22.8) | .346 |
| Sputum neutrophil, % | 12.7 (1.7-19.7) | 30.0 (12.0-36.3) | 10.7 (2.4-23.8) | .544 |
| PB eosinophil, % | 6.2 (2.2-13.4)[c] | 3.3 (1.5-6.3) | 3.2 (2.1-5.1)[c] | .049 |
| PB eosinophil count, cells/μL | 430.0 (170.5-1176.5)[c] | 234.0 (110.0-453.0) | 213.0 (130.0-341.5)[c] | .032 |
| Total serum IgE, IU/mL | 193.5 (89.0-349.5) | 226.0 (77.0-830.0) | 165.0 (63.0-364.5) | .856 |
| FEV1/FVC, % | 69.5 (12.6) | 49.7 (8.2) | 73.9 (12.4) | .328 |
| FEV1, % pred | 64.9 (22.1) | 49.8 (12.1) | 71.0 (19.8) | .334 |
| FVC, % pred | 76.3 (19.1) | 78.0 (10.6) | 80.4 (15.2) | .357 |
| Fixed obstruction, No. (%)[d] | 14 (35.0%)[a] | 6 (100.0%)[a,b] | 6 (25.0%)[b] | .003 |
| Controller medications, No. | 4.0 (2.5-4.0)[a] | 5.0 (5.0-5.0)[a,b] | 3.0 (2.0-4.0)[b] | .004 |
| Acute exacerbation in previous year, No.[e] | 1.0 (0.0-2.0) | 1.0 (1.0-3.0) | 1.0 (0.0-1.0) | .196 |
| Maintenance of oral corticosteroids, No. (%) | 23 (57.5%) | 5 (83.3%)[b] | 7 (29.2%)[b] | .021 |

Abbreviations: CT, computed tomography; $FEV_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; LA type, large or medium airway remodeling type; NN type, near-normal type; pred, predicted; PB, peripheral blood; SA type, small airway remodeling type.
Post hoc analysis was performed when the Kruskal-Wallis test, ANOVA, or Fisher exact test was positive (*P* value <.05) for continuous and categorical variables.
[a]Significant difference between LA and SA type.
[b]Significant difference between SA and NN type.
[c]Significant difference between LA and NN type.
[d]Fixed obstruction is defined as $FEV_1$ < 70% pred and $FEV_1$/FVC < 70% after treatment.
[e]Hospitalization and/or emergency department visits due to acute exacerbation of asthma in previous year.

common (24 patients, 26.4%), and SA (6 patients, 6.6%) was the least common type. Twenty-one patients (23.1%) exhibited a combination of the LA and SA types; LA was the predominant type (mLA) in 13 patients (14.3%), and SA was the predominant type (mSA) in 8 patients (8.8%).

Clinical characteristics were compared between patients with each of the 3 distinct phenotypes (Table 2). There were no significant differences between patients with different phenotypes in the following characteristics: age of onset, body mass index, atopic status, ratio of aspirin intolerance, total serum IgE level, and frequency of acute exacerbation during the previous year. The absolute count and percentage of peripheral blood eosinophils were significantly higher in patients with the LA phenotype, relative to patients with the SA or NN phenotypes (*P*=.032 and .049, respectively). There were no clear differences in clinical characteristics between LA and NN, such as disease duration, sex ratio, lung function, and the number of controller medications. However, the percentage of patients using oral corticosteroid maintenance therapy was significantly smaller in the NN type than in the LA or SA types. Relative to patients with the other 2 phenotypes, SA patients were more predominantly male and more likely to report being smokers; in addition, SA patients had a higher rate of fixed airflow obstruction (defined as $FEV_1$ <70% and $FEV_1$/FVC <70% despite appropriate asthma treatment), which was accompanied by the need for a greater number of controller medications and a higher rate of oral corticosteroid maintenance therapy. There was also weak statistical evidence

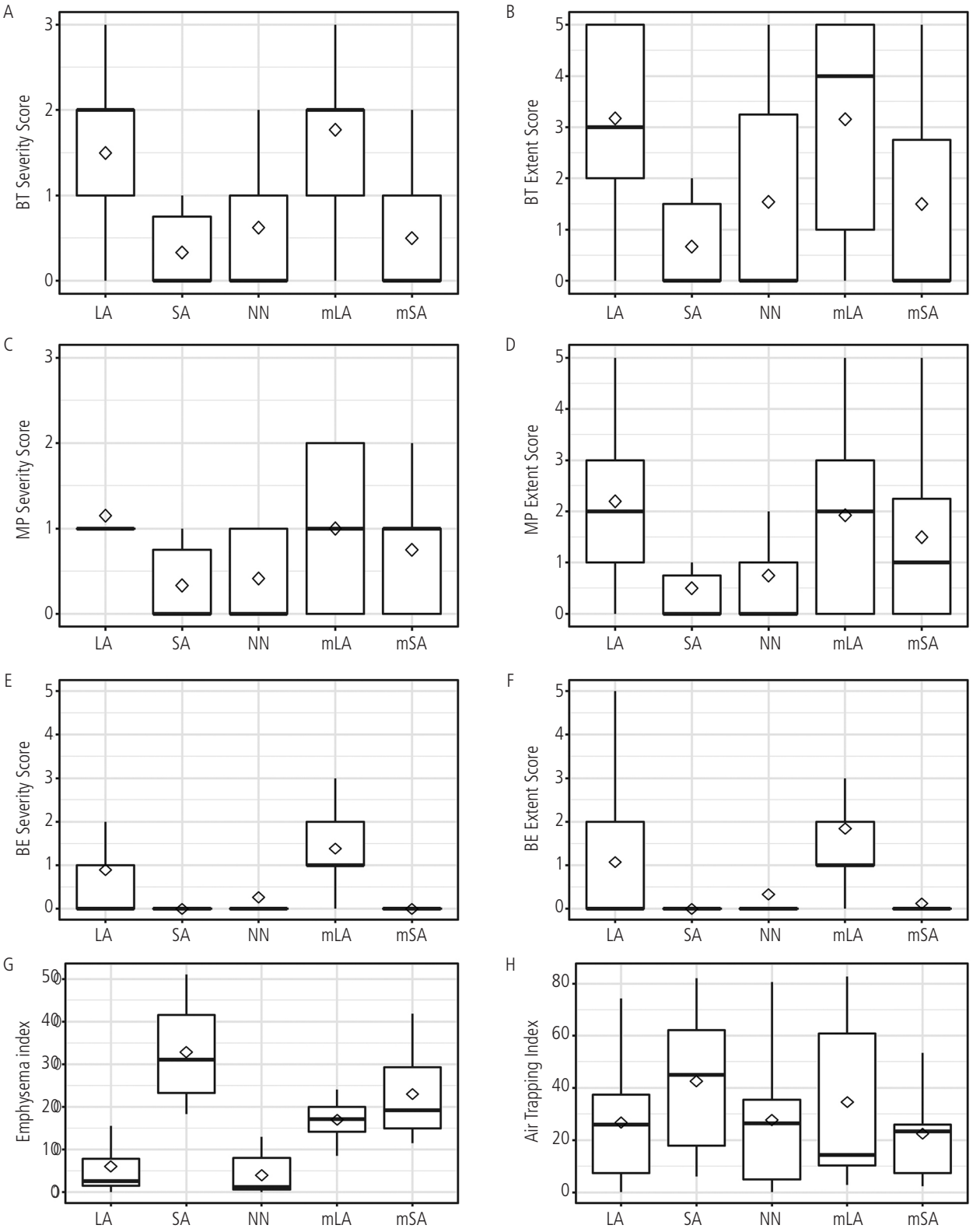


**Figure 2.** Comparison of the severity and extent of bronchial wall thickening (BT), mucus plugging (MP), and bronchiectasis (BE) with emphysema and air trapping index between computed tomography phenotypes. LA indicates large or medium airway remodeling type; SA, small airway remodeling type; NN, near-normal type; mLA, mixed type with a dominant pattern of large or medium airway remodeling; mSA, mixed type with a dominant pattern of small airway remodeling.

that these patients exhibited lower $FEV_1$/FVC and $FEV_1$ values, older age at the time of CT scan, and a longer duration of asthma than the other groups.

### *Semiquantitative Comparison of Phenotypes*

We performed a semiquantitative comparison of the emphysema index, the air trapping index, and the severity and extent of bronchial wall thickening, mucus plugging, and bronchiectasis between the phenotypes (Figure 2, Supplementary Table A). Patients with the LA type exhibited higher scores in both severity and extent of bronchial wall thickening, mucus plugging, and bronchiectasis. In contrast, SA patients had the highest index scores for both emphysema and air trapping, but the lowest levels of bronchial wall thickening, mucus plugging, and bronchiectasis. Little airway remodeling and few lung parenchymal changes were observed in patients with the NN type. Patients with the mLA type had CT index scores similar to those of patients with the LA type, with the exception of a higher emphysema index in patients with the mLA type. Likewise, there was weak statistical evidence that the scores associated with airway parameters (eg, bronchial wall thickening and mucus plugging) in patients with the mSA type demonstrated a higher trend than those of patients with the SA type; conversely, the emphysema index was similar in both groups. There was no significant difference in the air trapping index between any of the phenotypes.

## Discussion

We observed various abnormal radiologic findings in patients with severe asthma; these included bronchial wall thickening, mucus plugging, bronchiectasis, emphysema, and air trapping. In this study, approximately 81% of the patients demonstrated at least 1 radiologic structural change in bronchial wall thickening, mucus plugging, or bronchiectasis. These findings were also reported in previous studies of severe asthma patients [8,14,15]. However, their clinical significance was not fully evaluated in these studies.

We found that the severity of bronchial wall thickening and the extent of mucus plugging were significantly correlated with peripheral blood eosinophil and sputum eosinophil count, respectively. Eosinophils are well known as major effector cells in lung tissue damage and airway remodeling processes; in asthma patients, eosinophils act through multiple mediators, including cationic proteins, lipid mediators, cytokines, chemokines, and growth factors [16,17]. Tissue damage can trigger excessive activation of repair mechanisms, which may then contribute to structural changes including angiogenesis, hyperplasia of fibroblasts, airway smooth muscle cells, and goblet cells [18].

Airway remodeling is frequently observed in patients with severe asthma [14,15]. Emerging data show that biologics targeting type 2 cytokines, which are associated with eosinophil activity, have become an important modality in the treatment of severe, refractory asthma [18-20]. Consistent with our results, Halder et al [21] reported that a 12-month treatment with an interleukin-5 antibody in patients with refractory eosinophilic asthma resulted in a significant reduction in CT-measured bronchial wall area and total area, accompanied by reductions in both blood and sputum eosinophil counts relative to placebo. However, the relationship between structural changes and cellular airway inflammation markers in asthma has not been consistently demonstrated in previous studies. Niimi et al [22] failed to find a relationship between airway wall thickness and serum eosinophil cationic protein levels. In their recent study, Gupta et al [23] were also unable to correlate proximal airway remodeling indices with sputum eosinophil or neutrophil levels. The possibility that these studies included asthma patients who exhibited various degrees of disease severity prevented an association from being detected between inflammation markers and airway remodeling, as assessed by CT.

LA type was a major phenotype of severe asthma in our study, with representative features of bronchial wall thickening and mucus plugging in CT images; however, the NN type did not exhibit any remarkable structural remodeling. Interestingly, although both phenotypes demonstrated distinct phenotypic characteristics on CT images, they were difficult to distinguish from one another based on clinical characteristics such as age, disease duration, sex ratio, smoking status, pulmonary function, acute exacerbation, and treatment patterns; the notable exception was a difference in peripheral blood eosinophils. Therefore, we speculated that severe asthma with predominately eosinophilic inflammation would be more prone to remodeling in large-to-medium airways, accompanied by structural changes in diffuse bronchial wall thickening and mucus plugging.

Structural changes in asthmatic airways occur not only in the large-to-medium airways, but also in small airways with airflow obstruction [24-26]. A clinical entity known as asthma-COPD overlap (ACO) is currently considered to be an important subtype of severe asthma; the clinical characteristics of ACO are consistent with those of the SA type in the present study [27-29]. Patients with the SA type were predominantly male and reported the highest smoking rates. Furthermore, in the present study population, SA-type patients had the most severely impaired lung function, with fixed airflow obstruction. They also required more controller medication and oral corticosteroid maintenance therapy than the other groups. However, distinguishing ACO from other subtypes of asthma can be problematic when based solely on clinical findings, particularly in patients with severe asthma. Even if the patient reports a smoking habit or exhibits fixed airflow obstruction, radiologic findings may reveal completely different forms of remodeling, such as LA and SA types, thereby suggesting that other underlying diseases may be concurrently involved. Although the diagnosis of ACO has not yet been clearly established, morphological investigation via CT imaging can help to identify ACO among asthmatic patients.

CT imaging is a useful tool that provides valuable information on structural changes in the asthmatic lung. Since the early 1990s, various approaches have been used to characterize severe asthma phenotypes, and studies have been performed to compare airway structural changes between patients with uncomplicated asthma and either patients with COPD or healthy patients [30,31]. Some subgroups of patients with severe asthma have been identified through less biased, statistics-based methods [3-6]. Gupta et al [23] recently made

a notable attempt to use principal components and cluster analyses to determine asthma phenotypes that were based on airway structural changes visualized on CT images. The data provided by the authors indicated 3 asthma phenotypes with distinct clinical and radiologic features; more severe air trapping and proximal airway remodeling were found in 2 clusters, whereas proximal airway remodeling was not found in 1 cluster. However, the cluster analysis method is complex and is not easily applied in real-world contexts. In contrast, the visual analysis used in this study can be applied instantly in daily clinical practice. Moreover, our focus was not solely on the thickness of the bronchial wall, but included other common findings associated with asthmatic airway remodeling, such as mucus plugging, bronchiectasis, air trapping, and emphysema. In addition, segmental changes caused by bronchial wall thickening, mucus plugging, and bronchiectasis were assessed by grading the extent and severity of these conditions.

The major limitation of this study is the interval between CT scanning and clinical data collection. To minimize this time gap, we chose clinical data as close as possible to the time of the CT scan. Another important consideration is that airway remodeling might be the result of multiple pathogeneses instead of a uniform process; therefore, a distinct phenotype present as an outcome in our study might not belong to a specific clinical endotype. Further research, including molecular analysis, is in progress to assess this relationship between phenotypes and endotypes. Longitudinal study designs and molecular research in this field may advance the understanding of the mechanisms of severe asthma and enhance the approaches used to treat this condition.

Notwithstanding these limitations, our findings suggest that airway remodeling patterns can be categorized into diverse subtypes of severe asthma through CT imaging. We expect that CT findings, based on the site of airway involvement and remodeling pattern, can be used to determine 3 distinct phenotypes of severe asthma, which are indiscernible by clinical characteristics alone. In particular, proximal airway remodeling, including structural changes such as bronchial wall thickening and mucus plugging, may be used as an indicator of eosinophilic inflammation in severe asthma.

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*Conflicts of Interest*

The authors declare that they have no conflicts of interest.

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