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

Running title: CT scan classification of severe asthma

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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 by computed tomography (CT) images and to evaluate the clinical characteristics of individual image-based subtypes.

Methods: Chest CT images of 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), or bronchiectasis (BE). BT severity and MP extent score were independently associated with peripheral blood eosinophil count ($p = 0.012$, $r^2 = 0.112$) and sputum eosinophil count ($p = 0.022$, $r^2 = 0.090$), respectively. The large-to-medium airway remodeling type (LA type), showing diffuse BT combined with MP and BE, accounted for 44% of the total patients and revealed higher peripheral blood eosinophil counts than other types. The small airway remodeling type (SA type), which accounted for 6.6%, showed a higher rate of fixed airflow obstruction, along with male- and smoker-predominance and more controller medication use than other phenotypes. In 26% of patients with severe asthma, no prominent airway remodeling was observed (near-normal type, NN type); NN type showed less requirement for oral steroid relative to LA and SA types.

Conclusions: Three different structural types can be distinguished by chest CT findings, depending on the site of airway involvement and remodeling pattern in lungs of patients with severe asthma. Remodeling in large-to-medium sized airways revealed an association with systemic eosinophilic inflammation in 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 ($p = 0,012$, $r2 = 0,112$) y el recuento de eosinófilos en esputo ($p = 0,022$, $r2 = 0,090$), 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

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Introduction

Asthma, a common inflammatory airway disorder, is increasing in prevalence worldwide. Approximately 5–10% of asthma patients exhibit a severe form that is resistant to conventional treatment [1, 2], which can impose a substantial economic burden. Therefore, the study of severe asthma is an important and challenging area of research; this includes understanding its mechanisms, reducing related morbidity and healthcare costs, and developing effective treatments for the disorder. Emerging data from numerous studies strongly suggest that severe asthma is a syndrome of heterogeneous conditions. Thus, researchers have recently attempted to classify phenotypes of severe asthma, using clinically observable characteristics in a large-scale cohort [3-7].

Computed tomography (CT) scan is an ideal non-invasive modality to assess the distribution, extent, and severity of morphological changes in the airways and lung parenchyma. Although CT scan is not an essential diagnostic test for asthmatic patients, it helps to identify comorbid conditions, such as allergic bronchopulmonary aspergillosis and Churg-Strauss syndrome, as well as to detect diseases that mimic asthma. In a large cohort study, approximately 80% of patients with severe asthma showed abnormalities in the chest CT images, which suggested 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 airways and lung parenchyma, are not yet 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 purpose of this study was 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

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remodeling patterns visible in CT images.

Materials and methods

Study subjects

A single-center, retrospective study was conducted using data of patients with severe asthma who were followed up at an allergy clinic in a tertiary care hospital for at least one 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 two allergy specialists, based on the patient's medical history and the presence of at least one of the following criteria: (1) bronchodilator reversibility, characterized by an increase in the forced expiratory volume in one second (FEV_1) that was >12% and >200 mL from baseline following the inhalation of 400 μg of salbutamol; or (2) a positive response to a methacholine inhalation challenge, which was defined as provocative concentration causing 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 anti-asthmatic treatment for at least one 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 multi-detector CT scanner (Ingenuity, Philips Healthcare), under full inspiration and full expiration. CT parameters were as follows: 200 reference mAs, 120 kVp, 1.0 mm reconstruction thickness, 1.0 mm reconstruction increment, YC0 reconstruction filter, 0.5 sec rotation time. All CT scans were evaluated by two 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 (BT), mucus plugging (MP), bronchiectasis (BE), and lung parenchymal changes were analyzed. The extents of BT, MP, and BE were evaluated as the number of involved lobes (range: 0–5). The severities of these parameters were assessed on a 4-point scale, ranging from 0 to 3 (0, no abnormality; 1, partial non-continuous BT and BE/bronchial obstruction of mucus; 2, diffuse continuous BT/MP/BE; 3, diffuse continuous lesions that extended to the subpleural area). The air trapping index and emphysema index were respectively defined 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 sub-segmental bronchi were involved, then the classification was large or medium airway remodeling type (large airway involvement, LA type); (2) if airways distal to the sub-segmental 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

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identification of emphysema or air trappings) [12]. Two thoracic radiologists agreed on each classification after considering the extent to which the lobes were involved in the case.

Statistical analysis

Continuous variables were summarized as median with interquartile range or mean ± standard deviation (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 $p < 0.1$ in simple linear regression model were adjusted in multiple linear regression analysis. To compare the continuous variables comprising clinical characteristics and CT indices, we performed the ANOVA or Kruskal-Wallis tests, following evaluation of whether or not the variables exhibited a normal distribution. Fisher's exact test was used to compare categorical variables. Differences were considered to be significant if the p value was < 0.05. If the Kruskal-Wallis test resulted in a p value < 0.05, pairwise comparisons of subgroups were performed using MedCalc version 13, in accordance with Conover's method [13]. Post-hoc analysis between subgroups was performed for significant categorical variables using Fisher's exact test, in which a p value of 0.017 was considered to indicate statistical significance (following Bonferroni correction). All statistical analyses, except pairwise comparisons after Kruskal-Wallis test, were performed with SPSS version 23.

Results

Clinical and CT-based characteristic findings for severe asthma patients

Among a total of 91 severe asthma patients who satisfied the inclusion criteria during the study period, BT was observed in 60 patients (65.9%), MP in 57 patients (62.6%), and BE in 32 patients (35.2%). Seventy-four patients (81.3%) exhibited at least one of these findings. The mean emphysema index was 12.6 ± 12.9%, whereas the mean air trapping index was

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29.9 ± 26.3%.

We evaluated the correlation between clinical features and CT parameters, such as the extent and severity score of BT, MP, BE, emphysema index, and air trapping index. Although BT severity demonstrated a significant positive correlation with peripheral blood eosinophil count (p = 0.042, r = 0.216), it was not associated with sputum eosinophil count (p = 0.981, r = –0.003). There was an inverse correlation between BT severity and sputum neutrophil count (p = 0.048, r = –0.261). The extent of BT was not significantly associated with clinical parameters. Although there were no significant correlations between MP severity and other clinical characteristics, the extent of MP demonstrated a positive correlation with sputum eosinophil percentage (p = 0.027, r = 0.288).

A greater extent of BE was associated with a lower FEV_1 (% predicted) (p = 0.039, r = –0.217), and BE severity was worse in non-smokers (p = 0.02, r = –0.287). The severity and the extent of BE were significantly higher in female patients (p = 0.007, r = 0.324; p = 0.046, r = 0.210).

The emphysema index was positively correlated with age (p = 0.032, r = 0.260), smoking history (p = 0.004, r = 0.354), male sex (p = 0.017, r = –290), and sputum neutrophilia (p = 0.020, r = 0.341), whereas it was negatively correlated with FEV_1 (% predicted) (p = 0.005, r = –0.338), FEV_1/FVC (%) (p < 0.001, r = –0.490), and blood eosinophil count (p = 0.049, r = –0.243). 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 < 0.10 in simple linear regression models), BT severity remained independently associated with peripheral blood eosinophil count (p = 0.012, r^2 = 0.112). MP extent was still

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significantly associated with sputum eosinophil count (%) (p = 0.022, r^2 = 0.090). BE extent score was higher in female patients and in patients with lower FEV_1 (p = 0.004 in both, r^2 = 0.137), but BE severity scores were significantly higher only in female patients (p=0.010, r^2=0.103). The emphysema index was significantly associated with smoking and low FEV_1/FVC (%) after adjustment (p = 0.023 for smoking; p = 0.002 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 airways and lung parenchyma of severe asthmatic patients could be classified into three distinctive categories with the consensus of two radiologists: LA, SA, and NN types (Figure 1). The traits of the LA type included diffuse BT combined with MP and BE, whereas those of the SA type included prominently low attenuation in the CT image of the lung, but no evidence of MP. 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 by their dominant pattern into mLA (mixed type with a dominant pattern of large or medium airway remodeling) or mSA types (mixed type with a dominant pattern of small airway remodeling).

Among the 91 subjects in this study, 70 subjects could be categorized into one of the three phenotypes; the LA type was the most common (40 patients, 44.0%); NN was the second-most common (24 patients, 26.4%), and SA (six patients, 6.6%) was the least common type. Twenty-one patients (23.1%) exhibited a combination of LA and SA types; LA was the predominant type (mLA) in 13 patients (14.3%), and SA was the predominant type (mSA) in eight patients (8.8%).

Clinical characteristics were compared among patients with each of three distinct

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phenotypes (Table 2). There were no significant differences among patients with different phenotypes in the following characteristics: age of onset, BMI, atopic status, ratio of aspirin intolerance, total serum IgE level, or frequency of acute exacerbation during previous year. The absolute count and percentage of peripheral blood eosinophils were significantly higher in patients with LA type, relative to patients with SA or NN types (p=0.032 and 0.049, respectively). There was no clear difference in clinical characteristics, such as disease duration, sex ratio, lung function, and the number of controller medications, between LA and NN types. However, the proportion of patients using oral corticosteroid maintenance therapy was significantly smaller in the NN type, compared with the LA or SA types. Relative to patients with the other two phenotypes, patients with the SA type were more predominantly male and more likely to report being smokers; further, patients with SA type 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 a need for a greater number of controller medications and a higher rate of oral corticosteroid maintenance therapy. There was also weak statistical evidence that these patients exhibited lower FEV_1/FVC and FEV_1 values, an older age at the time of CT scan, and a longer duration of asthma than the other groups.

Semi-quantitative comparison of phenotypes

In a semi-quantitative manner, the emphysema index, the air trapping index, and the severity and extent scores of BT, MP, and BE were compared among the phenotypes (Figure 2, Supplementary Table A). Patients with the LA type exhibited higher scores in both severity and extent of BT, MP, and BE. In contrast, patients with the SA type demonstrated the highest index scores for both emphysema and air trapping, but had the lowest levels of BT, MP, and BE. Patients with the NN type demonstrated little airway remodeling and few lung

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parenchymal changes. Patients with the mLA type exhibited 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, such as BT and MP, of patients with mSA type demonstrated a higher trend than those of patients with SA type; conversely, there was a similar emphysema index in both groups. There was no significant difference in the air trapping index among any of the phenotypes.

Discussion

Various abnormal radiologic findings were frequently observed 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 one radiologic structural change in BT, MP, or BE. These findings were also reported in previous studies of severe asthma patients [8, 14, 15]. However, their clinical significance was not fully evaluated in those prior studies.

In this investigation, BT severity and MP extent demonstrated a significant correlation 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, as well as hyperplasia of fibroblasts, airway smooth muscle cells, and goblet cells [18].

Airway remodeling is frequently observed in patients with severe asthma [14, 15]. Biologics targeting type 2 cytokines, which are associated with eosinophil activity, have become an

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important modality in the treatment of severe, refractory asthma, on the basis of emerging data [18-20]. Consistent with our results, Halder *et al.* 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 [21]. However, the relationship between structural changes and cellular airway inflammation markers in asthma has not been consistently demonstrated in previous studies. Niimi *et al*. failed to find a relationship between airway wall thickness and serum eosinophil cationic protein levels [22]. Gupta *et al.* were also unable to correlate proximal airway remodeling indices with sputum eosinophil or neutrophil levels in their recent work [23]. Possibly, these studies might have included asthma patients who exhibited various degrees of disease severity; hence, an association could not be 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 BT and MP in CT images; however, the NN type did not exhibit any remarkable structural remodeling. Interestingly, although these two 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 of diffuse BT and MP.

Structural changes in asthmatic airways occur not only in the large-to-medium airways, but also in small airways with airflow obstruction [24-26]. Currently, a clinical entity known as asthma-COPD overlap (ACO) is considered to be an important subtype of severe asthma;

clinical characteristics of ACO accord with those of the SA type in our current study [27-29]. Patients with the SA type were predominantly male and reported the highest smoking rates. Furthermore, among all study subjects, SA-type patients revealed the most severely impaired lung function with fixed airflow obstruction; they also required more controller medication and oral corticosteroid maintenance therapy, relative to the other groups. However, distinguishing ACO from other subtypes of asthma can be problematic when solely utilizing clinical findings for separation, particularly in patients with severe asthma. Even if the patient reports a smoking habit or exhibits a fixed airflow obstruction, radiologic findings may reveal completely different forms of remodeling, such as LA and SA types, thereby suggesting that other underlying pathologies may be concurrently involved. Although the diagnosis of ACO has not yet been clearly established, morphological investigation via CT image can provide an important clue to distinguishing cases of ACO among asthmatic patients.

CT imaging is a useful tool that offers valuable information regarding structural changes in the asthmatic lung. Since the early 1990s, various approaches to characterize severe asthma phenotypes have been utilized, 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]. Recently, there was a notable attempt to use principle components and cluster analyses to determine asthma phenotypes that were based on airway structural changes visualized on CT images [23]. In that study, the data indicated three asthma phenotypes with distinct clinical and radiologic features; in two clusters, more severe air trapping and proximal airway remodeling were found, whereas in one cluster, proximal airway remodeling was not found. However, the cluster analysis method is complex and is not easily put to practical use in real-world applications. In contrast, the visual analysis used in this study can be instantly applied to daily clinical practice. Moreover,

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our focus was not solely on the thickness of the bronchial wall, but included other common findings associated with asthmatic airway remodeling, such as MP, BE, air trapping, and emphysema. In addition, segmental changes caused by BT, MP, and BE were assessed by grading the extent and severity of these conditions.

The major limitation of this study is the time gap 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, one distinct phenotype present as an outcome in our study might not belong to a specific clinical endotype. To study this relationship between phenotypes and endotypes, further research is in progress, including molecular analysis. Longitudinal study designs and molecular research in this field may advance the understanding of the mechanisms of severe asthma and enhance the therapeutic approaches for treating this condition.

Notwithstanding these limitations, this study suggests 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 three distinct phenotypes of severe asthma, which are indiscernible by clinical characteristics alone. In particular, proximal airway remodeling, including structural changes such as BT and MP, may be used as an indicator of eosinophilic inflammation in severe asthma.

Conflict of Interest: The authors of this manuscript declare no relevant conflicts of interest.

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Figure Legends

Figure 1. Representative images of each phenotype determined through computed tomography (CT): large or medium airway remodeling (LA) type (A), small airway remodeling (SA) type (B), and near-normal (NN) type (C).

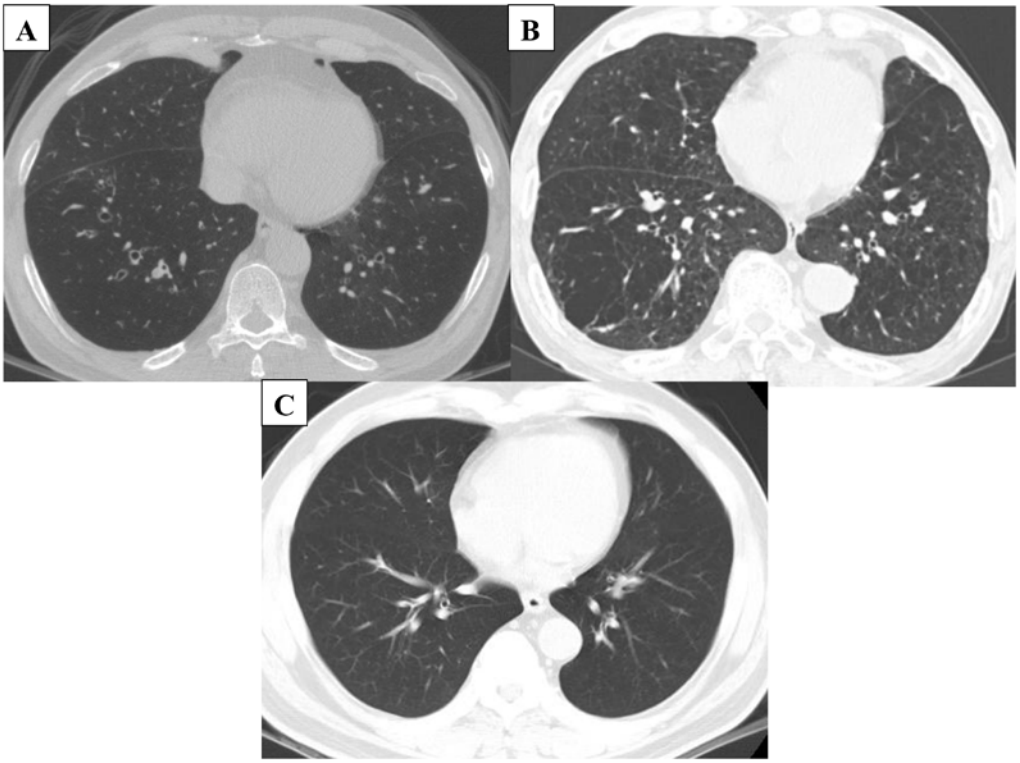

Figure 2. Comparison of the severity and extent score of bronchial wall thickening (BT), mucus plugging (MP), and bronchiectasis (BE) with emphysema and air trapping index between computed tomography (CT) phenotypes. Abbreviations: LA type, large or medium airway remodeling type; SA type, small airway remodeling type; NN type, 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.

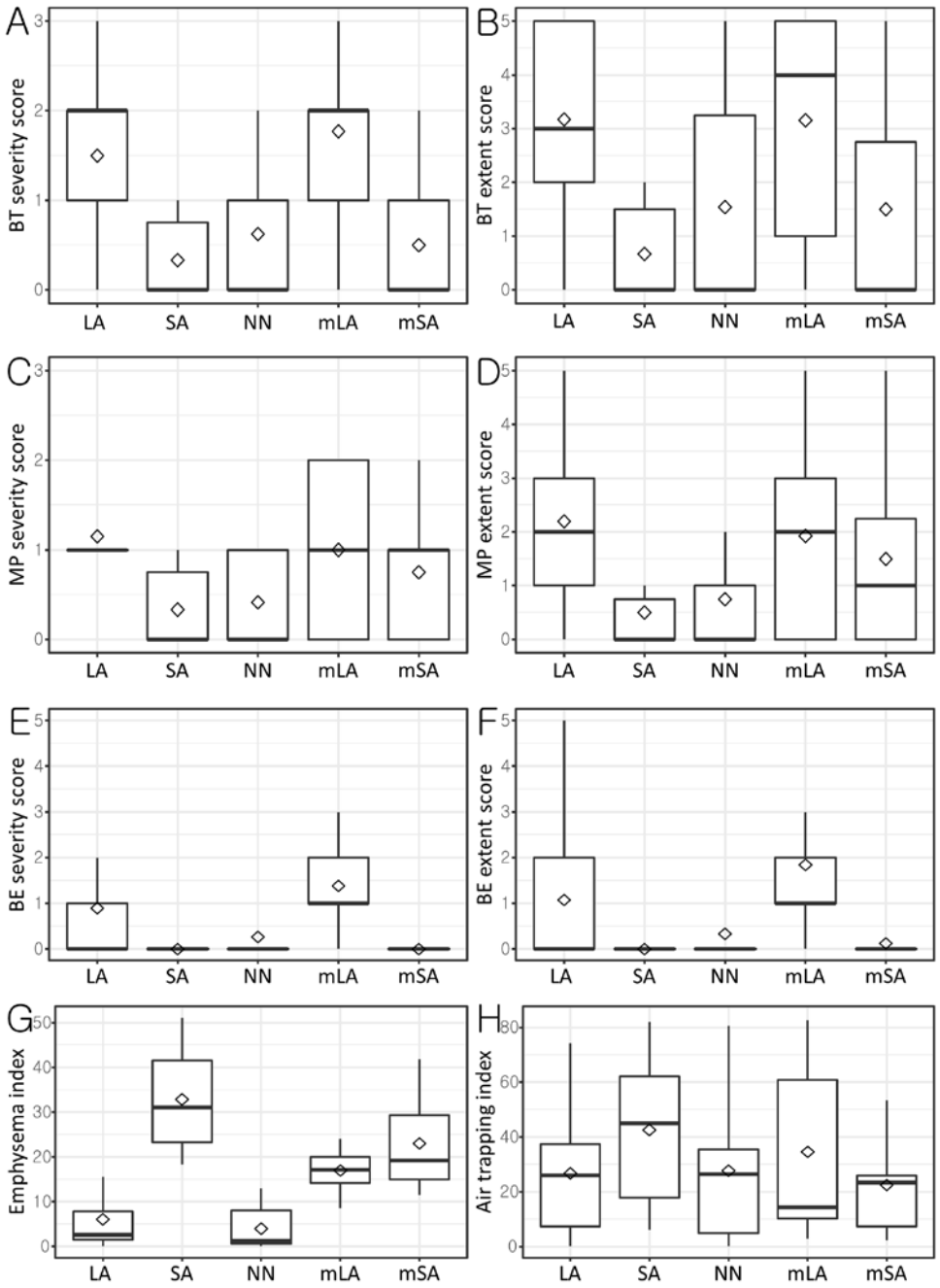

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Table 1. Results of multiple linear regression analysis between clinical indices and computed tomography (CT) findings

Dependent variables	Independent variables	Coefficient (β)	SE	*P-value*	R^2
BT severity score	PB eosinophil (cells/ μ L)	0.001	0.0002	0.012	0.112
MP extent score	Sputum eosinophil (%)	0.030	0.013	0.022	0.090
BE extent score	Sex: male (ref) vs. female	0.953	0.320	0.004	0.137
	FEV_1 (% predicted)	- 0.023	0.008	0.004	
BE severity score	Sex: male (ref) vs. female	0.726	0.272	0.010	0.103
Emphysema index (%)	Smoker: never (ref) vs current or previous	7.845	3.303	0.023	0.426
	FEV_1/FVC (%)	- 0.375	0.113	0.002	

Age, sex, and variables for which $p < 0.1$ in simple linear regression models were adjusted in multiple linear regression analysis.

Abbreviations: SE, standard error; BT, bronchial wall thickening; PB, peripheral blood; MP, mucus plugging; BE, bronchiectasis; ref, reference group; pred, predicted; FEV_1, first second of forced expiratory volume; FVC

Table 2. Comparison of clinical characteristics among individual phenotypes

	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]	0.640
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]	0.070
Disease duration (y)	16.0 [12.0;21.0]	26.0 [16.0;34.0]	12.5 [8.0;20.0]	0.078
BMI (kg/m2)	24.3 ± 3.8	20.8 ± 3.7	24.0 ± 2.7	0.656
Sex (n, %)				0.003
Male	13 (32.5%)*	6 (100.0%)*	14 (58.3%)	
Female	27 (67.5%)*	0 (0.0%)*	10 (41.7%)	
Smoking status (n, %)				0.003
Never-smoker	29 (72.5%)*	0 (0.0%)*†	15 (62.5%)†	
Ex- or current-smoker	11 (27.5%)*	6 (100.0%)*†	9 (37.5%)†	
Atopy (n, %)	20 (52.6%)	2 (33.3%)	11 (47.8%)	0.670
Sinusitis (n, %)	29 (72.5%)	1 (20.0%)	14 (60.9%)	0.061
Aspirin intolerance (n, %)	2 (5.0%)	0 (0.0%)	3 (12.5%)	0.411
Sputum eosinophil (%)	16.2 [5.3;25.7]	7.8 [3.0;12.0]	6.7 [3.2;22.8]	0.346
Sputum neutrophil (%)	12.7 [1.7;19.7]	30.0 [12.0;36.3]	10.7 [2.4;23.8]	0.544
PB eosinophil (%)	6.2 [2.2;13.4]‡	3.3 [1.5; 6.3]	3.2 [2.1; 5.1]‡	0.049

PB eosinophil count (cells/μL)	430.0 [170.5;1176.5]‡	234.0 [110.0;453.0]	213.0 [130.0;341.5]‡	0.032
Total serum IgE (IU/mL)	193.5 [89.0;349.5]	226.0 [77.0;830.0]	165.0 [63.0;364.5]	0.856
FEV_1/FVC (%)	69.5 ± 12.6	49.7 ± 8.2	73.9 ± 12.4	0.328
FEV_1 (% pred)	64.9 ± 22.1	49.8 ± 12.1	71.0 ± 19.8	0.334
FVC (% pred)	76.3 ± 19.1	78.0 ± 10.6	80.4 ± 15.2	0.357
Fixed obstruction§ (n, %)	14 (35.0%)*	6 (100.0%)*†	6 (25.0%)†	0.003
Controller medications (n)	4.0 [2.5; 4.0]*	5.0 [5.0; 5.0]*†	3.0 [2.0; 4.0]†	0.004
Acute exacerbation in previous year‖ (n)	1.0 [0.0; 2.0]	1.0 [1.0; 3.0]	1.0 [0.0; 1.0]	0.196
Maintenance of oral steroid (n, %)	23 (57.5%)	5 (83.3%)†	7 (29.2%)†	0.021

Post-hoc analysis was performed when the Kruskal-Wallis test, ANOVA or Fisher's exact test was positive (p-value < 0.05) for continuous and categorical variables. *significant difference between LA and SA type; † between SA and NN type; ‡ between LA and NN type

§Fixed obstruction is defined as FEV_1 < 70% pred and FEV_1/FVC < 70% after treatment.

‖ Hospitalization and/or emergency department visits due to acute exacerbation of asthma in previous year

Abbreviations: LA type, large or medium airway remodeling type; SA type, small airway remodeling type; NN type, near-normal type; pred, predicted; PB, peripheral blood; CT, computed tomography; FEV_1, first second of forced expiratory volume; FVC