Airway reactance predicts static lung hyperinflation in severe asthma

Running Title: Hyperinflation in severe asthma

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Abstract

Background: Static lung hyperinflation (SLH) measured by body plethysmography (Pleth) in asthma is associated with poor outcomes. The severity of SLH may be associated with small airway dysfunction (SAD), which can be measured by impulse oscillometry (IOS).

Objective: This study aims to determine the correlation between SLH and SAD in patients with severe asthma and the improvement of SLH and SAD in response to treatment.

Methods: We analyzed data from patients who were enrolled in the Taiwan Severe Asthma Registry, which was a prospective observational cohort. Pleth and IOS were regularly performed. The relationship between spirometric and IOS parameters was determined. Changes in the clinical outcomes in response to treatment were analyzed.

Results: In 107 patients with severe asthma, 83 (77.6%) had SLH by increased residual volume to total lung capacity (RV/TLC) ratio. Most patients were older female with worse pulmonary function and SAD compared with those without SLH. The SAD by increased airway resistance/reactance was significantly correlated with SLH. Airway reactance at 5 Hz (X_5) ≤ −0.21 [kPa/(L/s)] detected SLH with the area under the receiver operating characteristic curve of 0.84 ($p < 0.0001$, sensitivity = 85.2%, and specificity = 83.3%). After 12 months, patients who received add-on biologics treatment had significantly reduced exacerbation, fractional exhaled nitric oxide level, blood eosinophil counts, improved forced expiratory volume in the first second, X_5, and a trend of reduced RV/TLC ratio compared with those without biologics treatment.

Conclusion: In severe asthma, airway reactance X_5 could be a novel parameter to assess SLH.

Key words: Body plethysmography. Impulse oscillometry. Static lung hyperinflation. Severe asthma.

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Resumen

Antecedentes: En el asma bronquial, la hiperinsuflación pulmonar estática (SLH) medida mediante pletismografía corporal (Pleth) se asocia a un peor pronóstico. La gravedad de la SLH podría estar asociada con la disfunción de las vías respiratorias pequeñas (SAD), que puede medirse mediante la oscilometría de impulsos (IOS).

Objetivo: Este estudio pretende determinar la correlación entre el SLH y la SAD en pacientes con asma grave y la mejora de ambos parámetros en respuesta al tratamiento.

Métodos: Se analizaron los datos de los pacientes que se inscribieron en el Registro de Asma Grave de Taiwán, una cohorte observacional prospectiva. Se realizaron periódicamente mediciones de Pleth e IOS. Se determinó la relación entre los parámetros espirométricos e IOS. Se analizaron los cambios en los parámetros clínicos y funcionales en respuesta al tratamiento.

Resultados: De una muestra de 107 pacientes con asma grave, 83 (77,6%) presentaban SLH, definida mediante una relación volumen residual/capacidad pulmonar total (VR/CTP) aumentada. La mayoría de los pacientes eran mujeres de edad avanzada con peor función pulmonar y SAD, en comparación con los que no tenían SLH. El SAD por aumento de la resistencia/reactancia de las vías respiratorias se correlacionó significativamente con el SLH. La reactancia de las vías respiratorias a 5 Hz (X5) ≤ -0,21 [kPa/(L/s)] detectó el SLH con un área bajo la curva ROC de 0,84 ($p < 0,0001$, sensibilidad = 85,2% y especificidad = 83,3%). Después de 12 meses, los pacientes que recibieron tratamiento biológico adicional presentaron una reducción significativa de las exacerbaciones, del nivel de óxido nítrico exhalado, del recuento de eosinófilos en sangre, una mejora del volumen espiratorio forzado en el primer segundo, de la X5, y una tendencia a la reducción del cociente RV/TLC en comparación con los que no recibieron tratamiento biológico.

Conclusiones: En el asma grave, la reactancia de la vía aérea X5, podría ser un parámetro novedoso para evaluar el SLH.

Palabras clave: Pletismografía corporal. Oscilometría de impulsos. Hiperinsuflación pulmonar estática. Asma grave.

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Introduction

Asthma is characterized by chronic airway inflammation and remodeling that mainly involves in the small airways [1-3]. Small airway dysfunction (SAD) can be detected by various methods [4], and up to 90.7% asthmatic patients have SAD with increased prevalence in more severe diseases [5,6]. In addition, asthmatic patients with SAD is associated with poor symptom control, more exacerbation, and increased use of oral corticosteroid [5,6]. A recent study from Severe Asthma Research Program-3 showed that SAD is associated with future lung function decline in patients with severe asthma [7].

Asthmatic patients with static lung hyperinflation (SLH) have higher wheezing frequency and increased needs of rescue medication [8]. Emerging evidence showed that SLH determined by increased low-attenuation area by computed tomography (CT) is associated with fixed airflow limitation, accelerated forced expiratory volume in the first second (FEV_1) decline, and future exacerbation in asthma, suggesting its impact on airway remodeling and parenchymal destruction [7,9]. SLH is defined as an increased volume of air trapped in the lung at the end of expiration due to the premature closure of small airways, which is more commonly determined by increased residual volume to total lung capacity (RV/TLC) ratio in body plethysmography [10,11]. Previous study showed that RV/TLC ratio is negatively correlated with FEV_1 in adult patients with obstructive lung disease [12]. In our prior study, we observed that increased small airway resistance and reactance are significantly associated with lower FEV_1 [13]. The relationship between

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hyperinflation and small airway function deserves further investigation.

Body plethysmography, which is used to measure lung volume, expiratory flow, and airway resistance, is effort-dependent and requires patients' cooperation with forced expiration. It could be challenging for some asthmatic patients who are elderly or have poor lung function. Impulse oscillometry (IOS) uses oscillation technique that measures lung mechanics in an effort-independent manner by applying different sound waves with various frequencies to assess airway resistance and reactance during tidal breathing [14-18]. SAD had been reported to be associated with important asthma outcomes, such as asthma control and exacerbation [19]. Compared with spirometry, IOS is more sensitive in identifying SAD in asthma [5,20]. Nevertheless, whether IOS could be a possible method to evaluate SLH in patients with severe asthma is still uncertain.

In this observational study for patients with severe asthma, we aimed to determine the relationship between hyperinflation and small airway function. Changes in small airway function and hyperinflation after global initiative for asthma (GINA) [21]-guided treatment were assessed as well.

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Methods

Ethic statement

This study was conducted at Taipei Veterans General Hospital and approved by the Institutional Ethical Review Board (IRB) of Taipei Veterans General Hospital (IRB-TPEVGH No.: 2019-07-035CC and 2022-04-007AC).

Study design and patients

We enrolled adult (≥20 years old) patients with severe asthma who underwent body plethysmography and IOS in Taipei Veterans General Hospital from July, 2019 to September, 2021 in outpatient setting. All patients were enrolled in the Taiwan Severe Asthma Registry, which is a prospective observational cohort with IRB approval. Severe asthma is defined by the criteria from the European respiratory society and American thoracic society (ERS/ATS) guideline [22]. All patients required steps 4-5 treatment recommended by the GINA report [21], including medium or high dose maintenance inhaled corticosteroid (ICS) and long-acting beta-2 agonist (LABA) with or without add-on long-acting muscarinic antagonists (LAMA) or leukotriene modifier/theophylline, or maintenance oral corticosteroid. The exclusion criteria included patients' age younger than 20 years; mild to moderate persistent asthma, combined with chronic obstructive pulmonary disease (COPD) or other pulmonary diseases, stage IV lung cancer, or end-stage malignancy; need for long term oxygen for more than 15 hours a day or non-invasive positive-pressure ventilation support for a least 6 hours a day; with active tuberculosis or other infectious diseases; or inability to answer the

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consent form.

IOS, body plethysmography and spirometry

The protocols of IOS, body plethysmography and spirometry have been previously described in detail [23]. In brief, the patients underwent IOS based on the standardized protocol from the manufacturer (Jaeger MS-IOS® Germany) and recommendations from ERS [14,15]. The confounding factors, like cheek vibration or air escaping from nose, were adjusted by nasal clips and cheek compression by hands. The patients were asked to tidally breath for 30 to 45 seconds without tongue interposition or glottis contraction during activation of the loudspeaker. The loudspeaker released around 120 to 150 pulses with a frequency from 5 to 35 Hz during the test time and superimposed the normal tidal breathing. For avoidance of the effect of forced expiration, IOS was arranged before the body plethysmography and spirometry [15]. Body plethysmography and spirometry were conducted under standardization and interpreted according to strategies from ATS/ERS [24-27]. For data analysis, we used two flow-sensing spirometers each linked to a computer (Jaeger MS-IOS®, Germany and Vmax 22 SensorMedics, Yorba Linda, CA, USA). For bronchodilator response (BDR) assessment, subjects were requested to avoid inhaled bronchodilator 12 h before the test. During bronchodilator test, spirometry was performed before and 15 min after 400 μg salbutamol (a short-acting beta-2 agonist, SABA) inhalation. A positive BDR was defined as an increase in FEV_1 or FVC for more than 12% and 200 mL from the baseline in response to a SABA.[24] All equipment were calibrated twice daily, and two independent pulmonologists were

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responsible for assuring the quality of the tests. SLH is defined by RV/TLC ratio more than 0.4 [11].

Data collection

Baseline demographic variables including age, gender, body mass index (BMI), smoking status, duration of asthma diagnosis, onset of asthma, comorbidities, medication, exacerbation history, asthma control test (ACT) score, blood eosinophil counts, fractional exhaled nitric oxide (FeNO) and peak expiratory flow rate (PEFR) were collected. IOS parameters including resistance at 5 Hz (R_5), the difference between resistance at 5 and 20 Hz (R_5-R_{20}), reactance at 5 Hz (X_5), resonant frequency (F_{res}), and area under reactance curve between 5 Hz and resonant frequency (AX) were recorded. The percentage (%) of predicted values of IOS parameters were also calculated [28]**.** Spirometric data including FEV_1, FVC, and forced expiratory flow between 25 and 75% of forced vital capacity ($FEF_{25-75\%}$) were obtained from the flow-volume curve of spirometry, and RV and TLC were calculated from the volume-time curve of body plethysmography. We also collected data from patients who completed 12 months follow-up to compare changes in these clinical parameters in response to treatment with or without biologics.

Statistical analysis

Kolmogorov-Smirnov goodness-of-fit test was used to assess the distribution of variables. Continuous variables are shown as mean ± standard deviation or median (interquartile range, IQR) according to its distribution. For different groups, the Student's *t*-test was performed for comparison of normally distributed variables and the Mann–Whitney *U* test was used for comparison of non-

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normally distributed data. Pearson's Chi-square test was applied for comparison of the categorical variables, which were shown as number (%). For changes in clinical parameters from baseline to 12 months follow-up, the McNemar's test and the Wilcoxon signed-rank test were used for comparing the categorical and the continuous variables, respectively. Spearman's rank correlation coefficient (r_s) was used to examine relationships between variables. To determine the capability of IOS parameters in detecting SLH outcome, we performed the receiver operating characteristic (ROC) curve analysis and calculated the optimal cutoff value by Youden index for discriminating the SLH outcome. A two-tailed *p*-value of less than 0.05 was considered significant. All analyses were carried out by SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) and MedCalc Statistical Software version 20.009 (MedCalc Software bv, Ostend, Belgium).

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Results

Baseline characteristics of patients

The study enrolled a total of 107 patients with severe asthma (**Figure 1**). **Table 1** demonstrated the baseline characteristics of the study subjects. Most patients were female (59.8%) with a median age of 68 years and BMI of 25.2 kg/m^2, 24.3% of patients were ever-smoker. The medium duration of asthma diagnosis was 17 years, and 60.7% of the study subjects were late-onset asthma [21,29]. There were 25.2% patients with atopy [30], 14% patients with allergic rhinitis, 11.2% patients with chronic rhinosinusitis, 3.7% patients had chronic rhinosinusitis with nasal polyps, 34.6% patients with gastroesophageal reflux disease, 5.6% patients with obstructive sleep apnea syndrome, 2.8% patients with anxiety, a median ACT score of 22, 65.4% patients had at least one exacerbation in the previous year, 76.6% patients took ICS/LABA/LAMA combination therapy, 40.2% patients took oral corticosteroid, 43.0% patients received biologics treatment, a median FeNO level of 30 ppb, and a median blood eosinophil count of 205 per μL. These patients were categorized into patients with and without SLH according to their RV/TLC ratio [11].

The majority of patients with severe asthma (n = 83, 77.6%) had SLH, and appeared to be older, more females and late-onset asthma, as well as less atopy in compared with patients without SLH, whereas the other characteristics showed no differences between groups.

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Baseline pulmonary function data of study subjects

Table 2 showed the baseline pulmonary function data of the patients. The patients had a medium peak expiratory flow rate (PEFR) of 250 L/min. The baseline FEV_1/FVC ratio, FEV_1 (% of predicted), FVC (% of predicted), $FEF_{25-75\%}$ and RV/TLC ratio of the patients were 62.9%, 64.7%, 79.3%, 27.4% and 0.50 respectively. Compared to patients without SLH, those with SLH had significantly lower PEFR, FEV_1/FVC, FEV_1 (% of predicted), FVC (% of predicted), $FEF_{25-75\%}$ and higher RV/TLC ratio.

The patients had a baseline R_5, R_5-R_{20}, F_{res}, X_5, and AX of 0.51, 0.17, 19.91, −0.27, and 1.79, respectively. Similarly, the absolute values of IOS parameters and % of predicted of X_5 were significantly worse in patients with SLH than those without SLH.

To elucidate the effect of age and gender, we analyzed characteristics of patients with or without SLH matched by age and gender from our cohort (**Table S1** in the Supplementary Material). A random number table was used to select patients from two groups for matching. First, we did a 1:1 match by gender, and therefore 24 patients from each group (8 females and 16 males) were selected. Then, patients were randomly selected by a 10-year grading scale in different genders, which resulted in 15 patients from each group shown in **Table S1**. The results still showed that patients with SLH had increased RV/TLC ratio and worse FVC compared to those without SLH. Of note, the IOS parameter X_5 (both absolute value and % of predicted value) were significantly worse in patients with SLH than those without SLH.

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Correlation between RV/TLC ratio and IOS measurements

Figure 2 shows that the absolute value of IOS parameters had moderate correlation with the RV/TLC ratio, the Spearman's rank correlation coefficient (r_s) of R_5-R_{20}, X_5, F_{res}, and AX were 0.48, -0.61, 0.45, and 0.57, respectively (all p values < 0.0001). **Figure S1** shows that among the IOS parameters presented by % of predicted values, only X_5 still had moderate correlation with the RV/TLC ratio (r_s=0.46, p<0.0001). **Figure S3** demonstrates the correlations between RV/TLC ratio and both absolute value and % of predicted values of R_5 and R_{20}. Similarly, the correlations were all weaker than those of X_5, either in absolute value (r_s= -0.61) or in % of predicted value (r_s= 0.46).

ROC curve analysis and optimal cut-off value

Figure 3 and **Table 3** demonstrate the ability of IOS parameters to detecting SLH which calculated by ROC curve analysis, yielding areas under the curve (AUC) of 0.84, 0.80, 0.75, and 0.74 for X_5, AX, R_5-R_{20}, and F_{res}, respectively (all p values < 0.0001). Among the four variables, X_5 showed the best performance in detecting SLH. The optimal cutoff value of X_5 was −0.21 [kPa/(L/s)] with a sensitivity of 85.2% and a specificity of 83.3%. **Figure S2** also showed that X_5 (% of predicted) had the highest AUC of 0.77 comparing with other IOS parameters in detecting SLH. **Figure S4** and **Table S2** demonstrate the ROC curves and the abilities to detect SLH by both absolute value and % of predicted values of R_5 and R_{20}. Similarly, the AUCs were all smaller than those of X_5, either in absolute value (AUC = 0.84) or in % of predicted value (AUC = 0.77).

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Baseline characteristics of patients with severe asthma with or without biologics treatment

Among all patients, 46 (43.0%) patients received biologics treatment, including 31 omalizumab (67.4%), 14 mepolizumab (30.4%) and one benralizumab (2.2%). The average time of biologics treatment before enrollment was 181.3 days with 95% of confidence interval of 96.7-266.0 days. **Table 4** indicates that patients who received biologics treatment had significantly lower BMI and ACT score, as well as more ever-smokers, comorbid with allergic rhinitis and anxiety, acute exacerbation (AE) number, and OCS use than those without biologics treatment. The other clinical characteristics and pulmonary function data had no between-group differences.

Changes in clinical characteristics after 12 months of treatment with or without biologics

Table 5 shows that 51 patients completed 12 months follow up, including 38 (74.5%) patients with SLH and 13 (25.5) patients without SLH. Twenty-five (49.0%) of them received biologics treatment, including 17 omalizumab (68.0%), 7 mepolizumab (28.0%) and 1 benralizumab (4.0%). The remaining 26 (51.0%) patients received standard treatment other than biologics according to the GINA guideline [21]. Patients who received biologics treatment had significantly more reduction in AE, FeNO, and blood eosinophil level; improved ACT score, FEV_1, and X_5; and a trend of reduced RV/TLC ratio ($p = 0.0520$) compared with those without biologics treatment.

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Discussion

In this study, a great proportion of patients with severe asthma had SLH. The features of these patients were older, female predominance, worse airflow obstruction, poor lung function and increased small airway resistance and reactance compared with those without SLH. We demonstrated that airway reactance X_5 measured by IOS can assess SLH in severe asthma with great sensitivity and specificity. It could be an alternative diagnostic measure in addition to body plethysmography which is effort-dependent and technically demanding. After 12 months of follow-up, patients who received add-on biologics treatment had significantly reduced exacerbation, FeNO, and blood eosinophil counts; improved asthma control, FEV_1, and X_5; and a trend of reduced RV/TLC ratio compared with those without biologics treatment.

The clinical characteristics of patients with SLH in our study were compatible with previous evidence indicating accelerated lung function decline and lower FEV_1 [7,12]. The consequences of SLH were shown to be associated with decreased inspiratory muscle function and exercise performance, more severe breathlessness, and impaired daily life activity regardless of asthma severity [31]. In severe emphysema, RV/TLC, an indicator of hyperinflation, was significantly correlated with 6-minute walking distance and symptom scores [32]. During 6-minute walking test, subjects with severe asthma had significantly reduced inspiratory capacity similar to the extent of subjects with COPD, indicating the development of dynamic hyperinflation [33]. In addition, increased RV% predicted was associated with frequent albuterol use and wheezing in patients with

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persistent asthma, suggesting a sign of unrelieved air trapping [8]. Besides, recent real-world evidence from the US CHRONICLE study, an observational cohort of United States adults with severe asthma, showed that females experienced more exacerbations and poorer symptom control [34]. Another international multi-database cohort study also demonstrated that patients with late-onset asthma were more frequently uncontrolled [35]. Taken together, the results from our study highlighted patients with severe asthma and SLH are an important phenotype which needs intensive management.

Similar to previous studies where SAD in asthma was associated with worse clinical outcomes [6,7], our data indicated that patients with SLH not only had poorer spirometric parameters but also more severe impaired small airway function measured by IOS. These functional parameters in the small airways including R_5-R_{20}, X_5, F_{res}, and AX were significantly correlated with FEV_1 and FVC as shown in our previous study [13]. In addition, increased airway resistance/reactance measured by IOS was significantly correlated with RV/TLC ratio. The results are consistent with those observed in patients with COPD, which also showed the significant correlation between R_5-R_{20}, F_{res}, X_5, and RV/TLC ratio [36]. While R_5 represents total airway resistance involving both large and small airways, R_{20} is a parameter measuring resistance from large airways, and therefore their difference (R_5-R_{20}) reflects resistance in the small airways [16]. **Figure S3**, **S4** and **Table S2** showed the absolute value of R_5 had more significant correlation with RV/TLC ratio and better ability to detect SLH than R_{20}, indicating the dominant effect of small airway resistance, also reflecting the nature

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of airway obstruction (medium FEV_1/FVC ratio of 62.9%) in our patients with severe asthma. Of note, X_5 demonstrated the best performance among these IOS parameters in detecting SLH in patients with severe asthma. The reactance (X) reflects the airway dissipation which responds to pulses delivered by loudspeaker with different pressure and frequencies, and is composed of both inertance and capacitance (the elasticity) [18]. The X_5 is the inertia and elasticity of the tissues of both small and large airways at 5 Hz [16,18]. Compared with other IOS parameters, our previous study showed that X_5 had the highest specificity to determine SAD in symptomatic patients with preserved pulmonary function [13]. Another study also found that the change in X_5, instead of airway resistance, was independently correlated with the volume change and gas trapping after methacholine challenge in asthmatic patients [37]. According to the equations to calculate the percentage of predicted values of IOS parameters, factors including gender, age, height, and weight must be considered [28]. After adjusting these factors, there is a significant difference in both X_5 and X_5 (% of predicted) between patients with or without SLH shown in **Table S1**. Besides, compared with other IOS parameters, both X_5 and X_5 (% of predicted) have stronger correlation with RV/TLC as well as better performance in detecting SLH for patients with severe asthma. In summary, SLH is associated with the degree of SAD and IOS parameter X_5 can provide supplementary information in the assessment of SLH.

Emerging evidence, as shown in our study, demonstrated that biologics targeting type 2 cytokines provided crucial benefits including reducing exacerbation and improving symptom

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control as well as lung function in patients with severe asthma [38,39]. Previous studies also showed that treatment of ICS and biologics improved SLH in patients with different severities of asthma [40,41]. Of note, our results showed a more significant improvement on X_5 than RV/TLC ratio after 12-month biologics treatment compared with those who did not receive biologics treatment. This finding is consistent with previous study that showed changes in IOS parameters after bronchodilator inhalation were more sensitive to spirometry in evaluating asthma control [20]. Moreover, a recent work by Shirai et al. showed that improvement of small airway function preceded FEV_1 change in patients who received benralizumab for their severe asthma [42]. Our results reinforced the role of IOS parameters, especially X_5, in evaluating SLH and treatment response after biologics in patients with severe asthma.

The study has several limitations. First, only patients who successfully completed body plethysmography were reviewed. The results await further validation in patients who cannot perform forced expiration in a prospective setting. Nevertheless, our study had shown the potential role of IOS as an alternative to body plethysmography in evaluating SLH in patients with severe asthma. Second, the number of patients who completed 12 months follow-up was small, and the 12-month treatment response may not reflect the long-term effects of treatment. However, our results highlighted the importance of IOS as a more sensitive tool to detect treatment responses in patients who received biologics.

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Conclusion

This study provides evidence that X_5 could be a potential surrogate for evaluation of SLH, which was traditionally assessed by body plethysmography. The improvement of X_5 could be a sensitive parameter indicating treatment response in patients with severe asthma.

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Conflicts of Interest

The authors declare that they have no conflict of interest related to this subject matter or materials discussed in this article.

Abbreviations

AX: Area under reactance curve between 5 Hz and resonant frequency

BMI: body mass index

FEV_1: Forced expiratory volume in the first second

$FEF_{25-75\%}$: Forced expiratory flow between 25 and 75% of forced vital capacity

FVC: Forced vital capacity

F_{res}: Resonant frequency

GINA: Global Initiative for Asthma

ICS: inhaled corticosteroid

IOS: Impulse oscillometry

R_5: Resistance at 5 Hz

R_{20}: Resistance at 20 Hz

R_5-R_{20}: Difference of R_5 and R_{20}

ROC curve: receiver operating characteristic curve

RV: Residual volume

SAD: Small airway dysfunction

SLH: Static lung hyperinflation

TLC: Total lung capacity

X: Reactance

X_5: Reactance at 5 Hz

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FIGURE LEGENDS

Figure 1. Flow chart of the study population. IOS, impulse oscillometry; SLH, static lung hyperinflation.

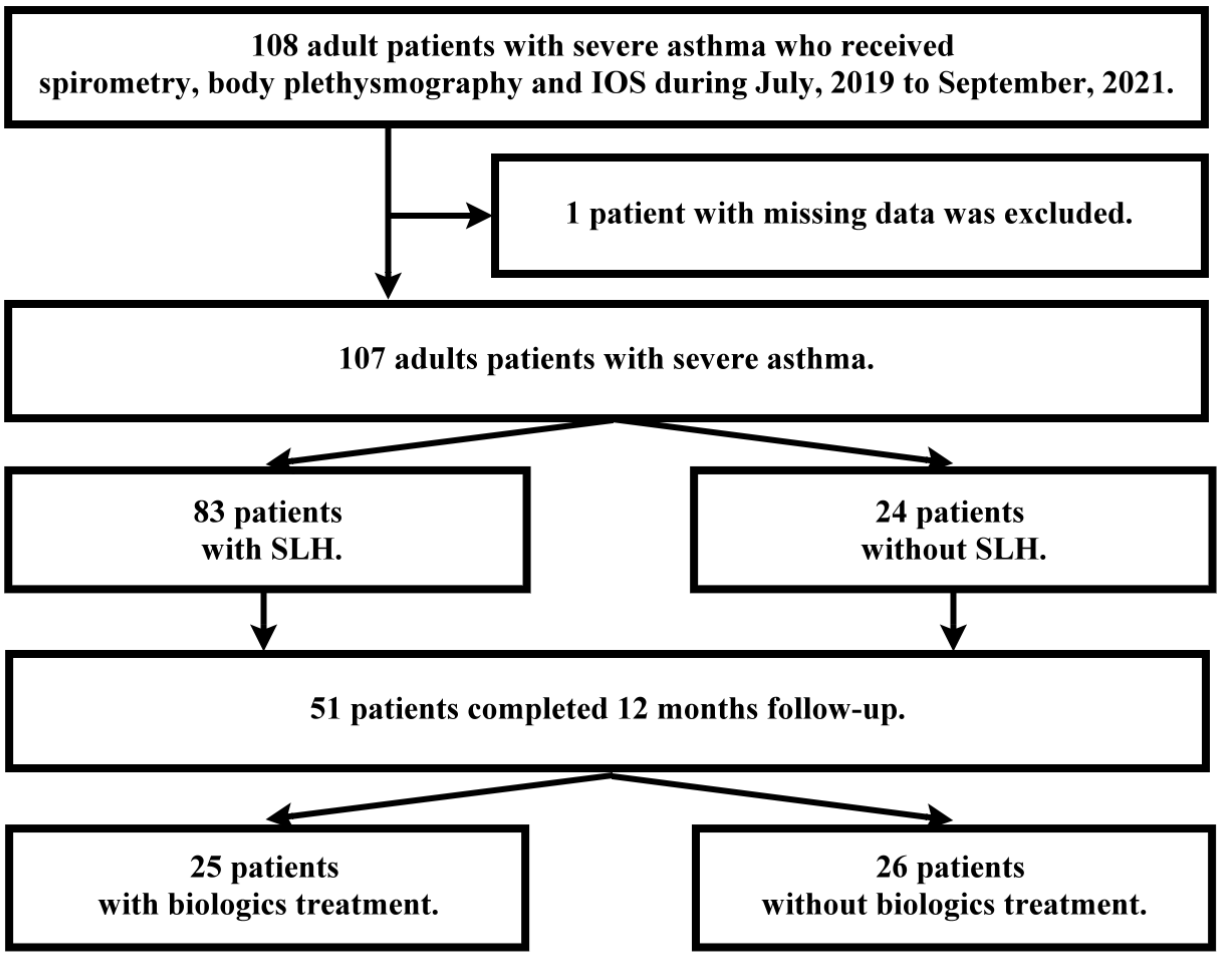

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Figure 2. Correlations between RV/TLC and impulse oscillometry parameters including **(A)** difference between resistance in 5Hz and 20Hz (R_5-R_{20}), **(B)** reactance in 5 Hz (X_5), **(C)** resonant frequency (F_{res}), **(D)** area under reactance curve between 5 Hz and resonant frequency (AX). RV, residual volume; TLC, total lung capacity.

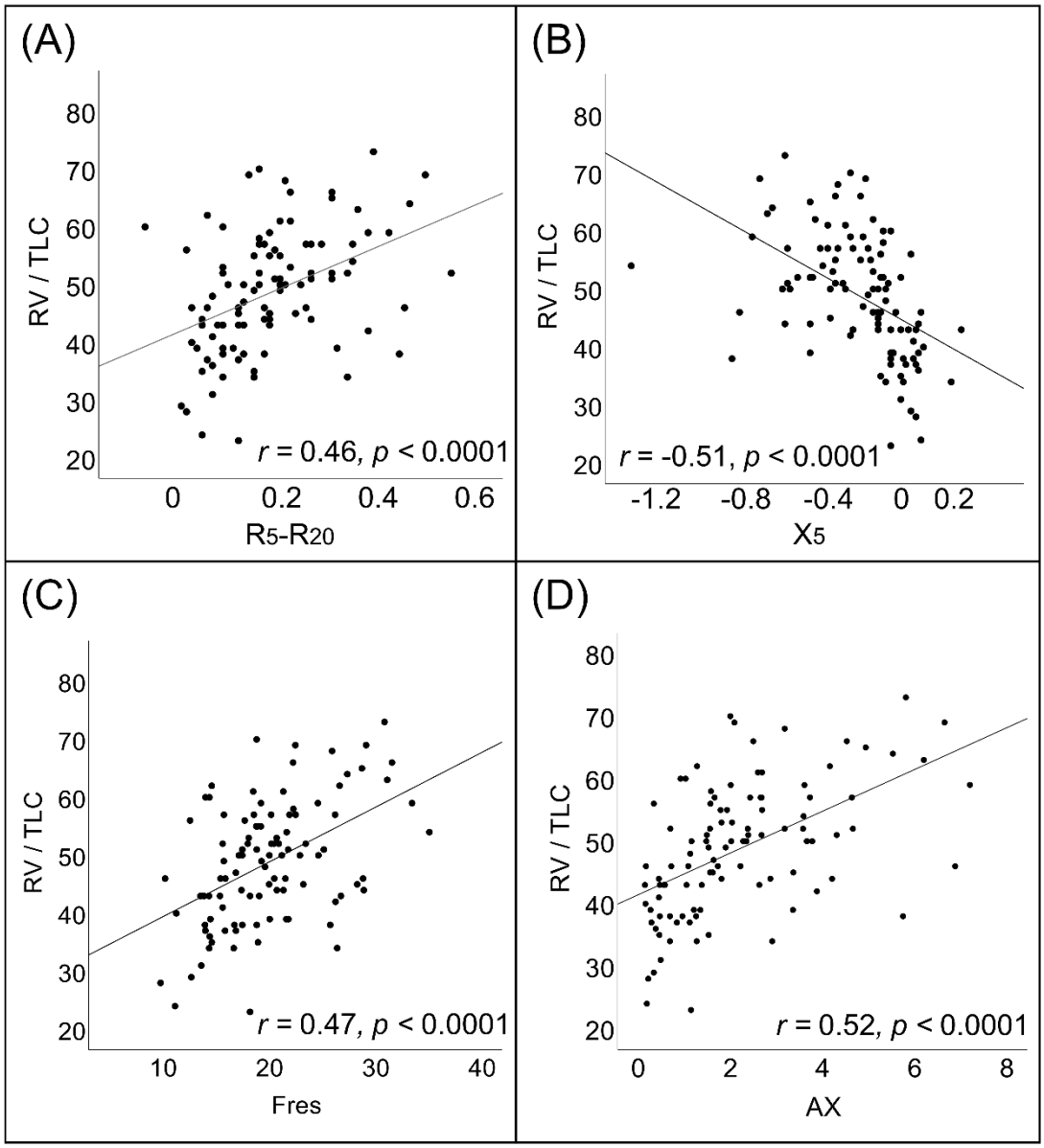

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Figure 3. Receiver operating characteristic curve analysis of impulse oscillometry parameters to detect static lung hyperinflation (SLH) in patients with severe asthma. R_5, resistance in 5 Hz; R_{20}, resistance in 20 Hz; X_5, reactance in 5 Hz; F_{res}, resonant frequency; AX, area under reactance curve between 5 Hz and resonant frequency.

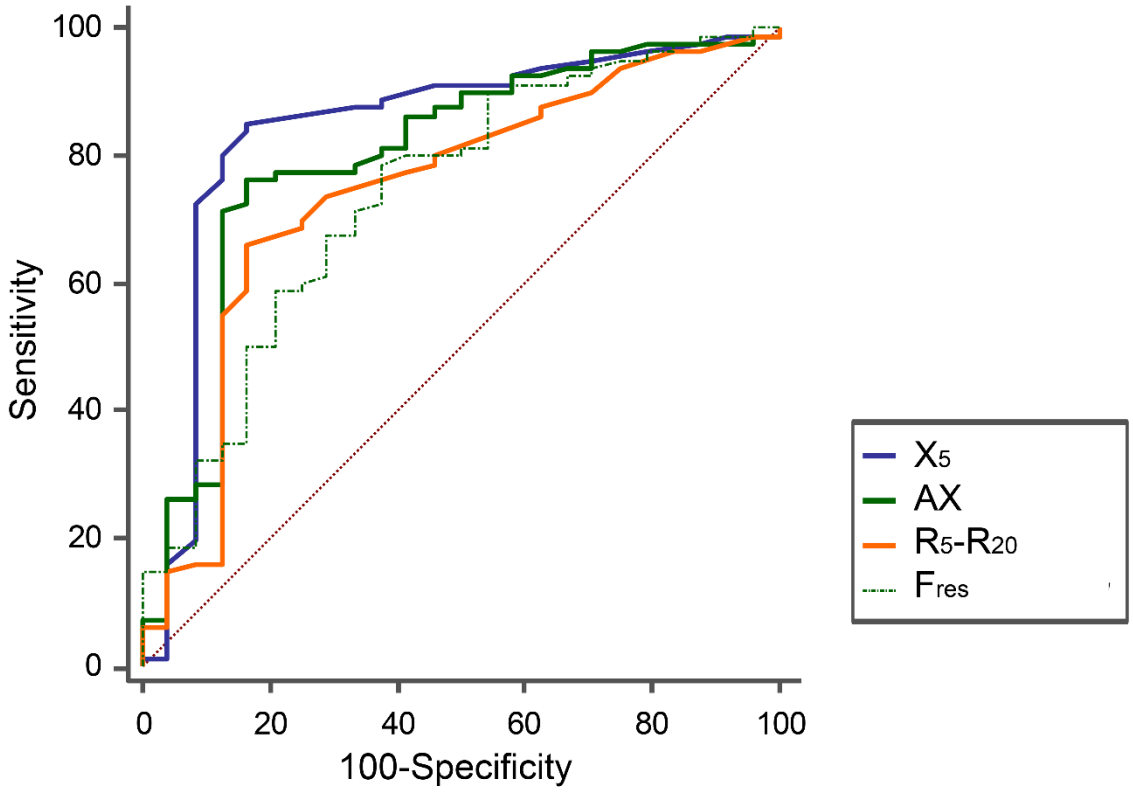

Table 1. Baseline characteristics of the study patients

	Total (n = 107)	Patients with SLH (n = 83)	Patients without SLH (n = 24)	*p* value
Female, N (%)	64 (59.8%)	56 (67.5%)	8 (33.3%)	**0.0028**
Age (year)	68 (55-77)	70 (61-78)	50 (40-65)	**< 0.0001**
BMI (kg/m^2)	25.2 (22.8-27.9)	25.2 (22.5-28.0)	25.3 (23.0-27.4)	0.9464
Ever-smoker, N (%)	26 (24.3%)	19 (22.9%)	7 (29.25%)	0.5298
Duration of asthma (years)	17.0 (6.8 - 34.0)	16.5 (6.0 - 40.0)	17.0 (7.0 - 31.5)	0.8072
Late-onset asthma, N (%)	65 (60.7%)	57 (68.7%)	8 (33.3%)	**0.0019**
Atopy, N (%)	27 (25.2%)	17 (20.5%)	10 (41.7%)	**0.0348**
Comorbidities, N (%)				
Allergic rhinitis	15 (14.0%)	10 (12.0%)	5 (20.8%)	0.2754
CRS	12 (11.2%)	7 (8.4%)	5 (20.8%)	0.0903
CRSwNP	4 (3.7%)	2 (2.4%)	2 (8.3%)	0.1784
GERD	37 (34.6%)	30 (36.1%)	7 (29.2%)	0.5268
OSAS	6 (5.6%)	5 (6.0%)	1 (4.2%)	0.7279
Anxiety	3 (2.8%)	1 (1.2%)	2 (8.3%)	0.0622
ACT score	22 (18-24)	22 (18-24)	22 (17-23)	0.4391
≥ 1 exacerbation/year, N (%)	70 (65.4%)	51 (61.4%)	19 (79.2%)	0.1082
Annual exacerbation number	1 (0-2)	1 (0 to 2)	1 (1 to 3)	0.1062
Medication				
Medium or high dose ICS/LABA/LAMA, N (%)	82 (76.6%)	63 (75.9%)	19 (79.2%)	0.7389
OCS, N (%)	43 (40.2%)	30 (36.1%)	13 (54.2%)	0.1129
Biologics, N (%)	46 (43.0%)	35 (42.2%)	11 (45.8%)	0.7506
FeNO (ppb)	30 (18-60)	32.5 (17-66)	29 (21.5-39.5)	0.5113
Blood eosinophil (/µL)	205 (98-338)	193 (102-356)	230 (92-304)	0.9494

SLH, static lung hyperinflation, defined as the ratio of residual volume (RV) to total lung capacity (TLC) ratio more than 0.4; BMI, body mass index; Late-onset asthma, defined as age of asthma onset ≥ 40 years old; atopy, defined as an increase in total immunoglobulin E >100 U/ml or a positive Phadiatop test result (>0.35 PAU/L); CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyps; GERD, gastroesophageal reflux disease; OSAS: obstructive sleep apnea syndrome; ACT, asthma control test; ICS/LABA/LAMA, inhaled corticosteroid, long-acting beta-2 agonist and long-acting muscarinic antagonist combination therapy; OCS, oral corticosteroid; FeNO, fractional exhaled nitric oxide; data are shown as number (%) for categorical variables and median (interquartile range, IQR) for non-normally distributed variables. *p* values were calculated by the Mann-Whitney *U* test and the values <0.05 were considered statistically significant.

Table 2. Baseline pulmonary function data of the study patients

	Total (n = 107)	Patients with SLH (n = 83)	Patients without SLH (n = 24)	*p* value
PEFR (L/min)	250 (180-345)	220 (170-300)	340 (20-470)	**< 0.0001**
Spirometry				
FEV_1/FVC (%)	62.9 (55.3-72.6)	62.1 (55.1-70.3)	69.8 (60.0-80.2)	**0.0358**
FEV_1 (% of predicted)	64.7 (52.9-78.3)	61.0 (49.8-70.0)	85.6 (66.1-95.1)	**0.0001**
FVC (% of predicted)	79.3 (69.6-88.6)	61.0 (49.8-70.0)	85.6 (66.1-95.1)	**0.0001**
$FEF_{25-75\%}$ (% of predicted)	27.4 (18.6-48.6)	24.0(18.0-39.5)	46.0(22.4-74.0)	**0.0109**
BDR (+), N (%)	19(17.8%)	14(16.9%)	5(20.8%)	0.6543
TLC (% of predicted)	98.5 (91.5-113)	98.0 (90.0-113.5)	105.5 (93.5-110.5)	0.4090
RV/TLC	0.50 (0.42-0.57)	0.52 (0.46-0.58)	0.37 (0.34-0.38)	**<0.0001**
Impulse oscillometry				
R5 [kPa/(L/s)]	0.51(0.42-0.67)	0.55(0.45-0.68)	0.43(0.36-0.48)	**<0.0001**
R5 (% of predicted)	165.2(133.9-198.6)	174.0(136.1-206.2)	139.2(131.2-175.1)	0.0749
R_5-R_{20} [kPa/(L/s)]	0.17 (0.01-0.26)	0.19 (0.13-0.27)	0.10 (0.07-0.15)	**0.0003**
R_5-R_{20} (% of predicted)	239.4(165.4-360.2)	262.4(164.5-367.7)	206.8(165.4-308.3)	0.4132
F_{res} (Hz)	19.91 (18.90-20.92)	20.2 (17.4-23.3)	16.3 (14.0-18.9)	**0.0003**
F_{res} (% of predicted)	136.3(118.5-164.4)	133.7(114.1-162.6)	150.3(128.4-183.5)	0.1012
X_5 [kPa/(L/s)]	-0.27 (-0.43 - -0.20)	-0.32 (-0.46 - -0.24)	-0.15(-0.20 - -0.10)	**< 0.0001**
X_5 (% of predicted)	245.6(172.2-358.1)	265.5(184.6-366.2)	173.1(109.0-226.0)	**<0.0001**
AX (kPa/L)	1.79 (1.03-2.30)	2.09 (1.46-3.58)	0.77 (0.36-1.27)	**< 0.0001**
AX (% of predicted)	422.4(246.5-700.2)	455.2(259.4-801.2)	320.6(201.9-602.4)	0.2031

SLH, static lung hyperinflation, defined as the ratio of residual volume (RV) to total lung capacity (TLC) ratio more than 0.4; PEFR: peak expiratory flow rate; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; $FEF_{25-75\%}$: forced expiratory flow between 25 and 75% of forced vital capacity; BDR (+), a positive bronchodilator response, defined as an increase in FEV_1 or FVC for more than 12% and 200 mL from the baseline in response to a short-acting beta-2 agonist; R_5, resistance in 5 Hz; R_{20}, resistance in 20 Hz; F_{res}, resonant frequency; X_5, reactance in 5 Hz; AX, area under reactance curve between 5 Hz and resonant frequency; data are shown as number (%) for categorical variables and median (interquartile range, IQR) for non-normally distributed variables. *p* values were calculated by the Mann-Whitney *U* test and the values <0.05 were considered statistically significant.

Table 3. Performance of different IOS parameters to detect SLH in patients with severe asthma

Variables	Cutoff value	Sensitivity (%)	Specificity (%)	LR (+)	LR (-)	AUC (95%CI)	Youden Index	*p* value
X_5 [kPa/(L/s)]	≤ -0.21	85.2	83.3	5.11	0.18	0.84 (0.76 - 0.91)	0.69	**<0.0001**
X_5 (% of predicted)	>189.39	75.9	75.0	3.04	0.32	0.77 (0.68- 0.85)	0.51	**<0.0001**
AX (kPa/L)	> 1.35	76.5	83.3	4.59	0.28	0.80 (0.71- 0.87)	0.60	**<0.0001**
AX (% of predicted)	>384.67	60.2	66.7	1.81	0.60	0.61 (0.52- 0.71)	0.27	0.0976
R_5-R_{20} [kPa/(L/s)]	> 0.16	66.3	83.3	3.98	0.41	0.75 (0.65-0.83)	0.50	**<0.0001**
R_5-R_{20} (% of predicted)	>224.89	60.2	70.8	2.07	0.56	0.62 (0.52- 0.71)	0.31	0.1023
F_{res} (Hz)	> 16.9	79.0	62.5	2.11	0.34	0.74 (0.65 - 0.82)	0.42	**<0.0001**
F_{res} (% of predicted)	≤154.01	74.4	45.83	1.38	0.55	0.59 (0.49- 0.68)	0.21	0.1612

IOS, impulse oscillometry; SLH, static lung hyperinflation, defined as the ratio of residual volume (RV) to total lung capacity (TLC) ratio more than 0.4; R_5, resistance in 5 Hz; R_{20}, resistance in 20 Hz; F_{res}, resonant frequency; X_5, reactance in 5 Hz; AX, area under reactance curve between 5 Hz and resonant frequency; LR (+), positive likelihood ratio; LR (-), negative likelihood ratio; AUC: area under the receiver operating characteristic curve. 95% CI: 95% of confidence interval.

Table 4. Baseline characteristics of the study patients with or without biologics treatment

	Total (n = 107)	Patients with biologics (n = 46)	Patients without biologics (n = 61)	*p* value
Female, N (%)	64 (59.8%)	27 (58.7%)	37 (60.7%)	0.8385
Age (year)	68 (55-77)	67 (51-78)	69 (56-75)	0.5007
BMI (kg/m^2)	25.2 (22.8-27.9)	24.1 (21.8-26.9)	26.0 (23.6-28.2)	**0.0482**
Ever-smoker, N (%)	26 (24.3%)	16 (34.8%)	10 (16.4%)	**0.0289**
Duration of asthma (years)	17.0 (6.8 - 34.0)	13.0 (7.0 – 25.0)	20.0 (5.0- 43.0)	0.2600
Late-onset asthma, N (%)	65 (60.7%)	32 (69.6%	33 (54.1%)	0.1239
Atopy, N (%)	27 (25.2%)	10 (21.7%)	17 (27.9%)	0.4702
Comorbidities, N (%)				
Allergic rhinitis	15 (14.0%)	10 (21.7%)	5 (8.2%)	**0.0464**
CRS	12 (11.2%)	3 (6.5%)	9 (14.8%)	0.1823
CRSwNP	4 (3.7%)	0 (0.0%)	4 (6.6%)	0.0774
GERD	37 (34.6%)	16 (34.8%)	21 (34.4%)	0.9689
OSAS	6 (5.6%)	3 (6.5%)	3 (4.9%)	0.7210
Anxiety	3 (2.8%)	3 (6.5%)	0 (0.0%)	**0.0434**
ACT score	22 (18-24)	20 (16-22)	22 (20-24)	**0.0010**
≥ 1 exacerbation/year, N (%)	70 (65.4%)	34 (73.9%)	36 (59.0%)	0.1094
Annual exacerbation number	1 (0-2)	2 (1-4)	1 (0-1)	**0.0002**
Medication				
Medium or high dose ICS/LABA/LAMA, N (%)	82 (76.6%)	37 (80.4%)	45 (73.8%)	0.4200
OCS, N (%)	43 (40.2%)	26 (56.5%)	17 (27.9%)	**0.0034**
FeNO (ppb)	30 (18-60)	33.5 (20-69)	28.5 (16.5-47)	0.2499
Blood eosinophil (/μL)	205 (98-338)	242 (103-339)	188 (94.8-315)	0.5584
PEFR (L/min)	250 (180-345)	255 (180-310)	245 (175-360)	0.9390
Spirometry				
FEV_1/FVC (%)	62.9 (55.3-72.6)	65.2 (54.3-72.9)	62.1 (55.9-71.6)	0.5333
FEV_1 (% of predicted)	64.7 (52.9-78.3)	65.6 (54.7-82.2)	64.0 (52.4-72.6)	0.4427
FVC (% of predicted)	79.3 (69.6-88.6)	79.3 (72.2-89.5)	79.0 (67.0-88.4)	0.5333
$FEF_{25-75\%}$ (%predicted)	27.4(18.6-48.6)	29.0(15.3-46.6)	27.2(20.0-50.8)	0.9839
BDR (+), N (%)	19 (17.8%)	10 (21.7%)	9 (14.8%)	0.3494
TLC (% of predicted)	98.5 (91.5-113)	98.5 (94.0-114.0)	98.5 (87.5-112.0)	0.3941
RV/TLC	0.50 (0.42-0.57)	50.0 (41.0-56.5)	48.5 (41.5-56.0)	0.6285
Impulse oscillometry				
R_5 [kPa/(L/s)]	0.51(0.42-0.67)	0.54(0.42-0.73)	0.51(0.41-0.65)	0.7321
R_5 (% of predicted)	165.2(133.9-198.6)	174.5(136.5-216.6)	161.7(132.7-193.4)	0.1502

R_5-R_{20} [kPa/(L/s)]	0.17 (0.01-0.26)	0.17 (0.10-0.28)	0.18 (0.12-0.25)	0.5836
R_5-R_{20} (% of predicted)	165.4(239.4-360.2)	280.3(151.6-391.2)	222.9(169.7-307.9)	0.4457
F_{res} (Hz)	19.91 (18.90-20.92)	19.5 (15.7-23.5)	18.9 (16.8-21.8)	0.7541
F_{res} (% of predicted)	136.3(118.5-164.4)	138.7(118.1-189.5)	134.8(117.7-154.4)	0.3232
X_5 [kPa/(L/s)]	-0.27 (-0.43 - -0.20)	-0.25 (-0.42 - -0.16)	-0.30 (-0.44 - -0.20)	0.3539
X_5 (% of predicted)	245.6(172.2-358.1)	247.4(152.0-350.5)	233.4(182.9-364.7)	0.6644
AX (kPa/L)	1.79 (1.03-2.30)	1.60 (0.70-3.58)	2.01 (1.10-2.90)	0.5038
AX (% of predicted)	422.4(246.5-700.2)	449.0(214.8-861.3)	409.1(266.0-619.2)	0.7773

Total 46 patients received biologics treatment for severe asthma, including omalizumab (n=31, 67.4%), mepolizumab (n=14, 30.4%), and benralizumab (n=1, 2.2%). BMI, body mass index; Late-onset asthma, defined as age of asthma onset ≥ 40 years old; atopy, defined as an increase in total immunoglobulin E >100 U/ml or a positive Phadiatop test result (>0.35 PAU/L); CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyps; GERD, gastroesophageal reflux disease; OSAS: obstructive sleep apnea syndrome; ACT, asthma control test; ICS/LABA/LAMA, inhaled corticosteroid, long-acting beta-2 agonist and long-acting muscarinic antagonist combination therapy; OCS, oral corticosteroid; FeNO, fractional exhaled nitric oxide; PEFR: peak expiratory flow rate; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; $FEF_{25-75\%}$: forced expiratory flow between 25 and 75% of forced vital capacity; BDR (+), a positive bronchodilator response, defined as an increase in FEV_1 or FVC for more than 12% and 200 Ml from the baseline in response to a short-acting beta-2 agonist; RV/TLC, the ratio of residual volume to total lung capacity ratio; R_5, resistance in 5 Hz; R_{20}, resistance in 20 Hz; F_{res}, resonant frequency; X_5, reactance in 5 Hz; AX, area under reactance curve between 5 Hz and resonant frequency; data are shown as number (%) for categorical variables and median (interquartile range, IQR) for non-normally distributed variables. *P* values were calculated by the Mann-Whitney *U* test and the values <0.05 were considered statistically significant.

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Table 5. Clinical characteristics among patients who completed 12 months follow-up

	With biologics treatment (n = 25)			Without biologics treatment (n = 26)		
	Baseline	12 months	*p* value	Baseline	12 months	*p* value
Female (%)	17 (68.0%)			15 (57.7%)		*0.4512
Age (year)	67 (56-77)			71 (66-76)		*0.2281
BMI (kg/m^2)	24.0 (21.9-27.9)			26.3 (24.1-28.5)		*0.0883
Smoking, N (%)	9 (36.0%)			3 (11.5%)		***0.0401**
ACT score	18 (14-21)	22 (20-23)	**0.0009**	23 (20-24)	23 (22-24)	0.2687
Annual exacerbation number	3 (1-4)	0 (0-1)	**0.0001**	1 (0-2)	0 (0-1)	**0.0138**
FeNO (ppb)	41 (23.0-108.5)	32.5 (14.0-45.5)	**0.0009**	29.0 (17.5-43.5)	22.5 (15.3-37.0)	0.6578
Blood eosinophil (/Ml)	316 (206-503)	129 (34-330)	**0.0032**	150 (81-261)	135 (78-250)	0.2309
PEFR (L/min)	260 (180-325)	305 (186-458)	0.3378	235 (158-373)	225 (140-375)	0.0887
Spirometry						
FEV_1/FVC (%)	63.1 (52.4-71.2)	71.6 (56.6-75.9)	0.2758	59.4 (55.8-71.8)	63.2 (55.5-71.9)	0.7533
FEV_1 (% of predicted)	65.0 (47.8-71.5)	71.0 (55.5-86.8)	**0.0102**	64.0 (56.3-79.0)	69.0 (57.4-82.0)	0.4692
FVC (% of predicted)	75.3 (66.0-88.9)	83.0 (71.7-91.7)	0.0875	83.9 (72.8-93.8)	85.5 (77.6-92.0)	0.5172
$FEF_{25-75\%}$ (%predicted)	23.0 (15.0-40.7)	34.0 (21.5-54.8)	0.3702	23.5 (17.8-50.5)	25.5 (18.0-43.8)	0.8194
BDR (+), N (%)	6 (24.0%)	2 (8.0%)	0.1019	4 (17.4%)	0 (0.0%)	**0.0457**
TLC (% of predicted)	98.0 (94.0-115.3)	101.0 (86.0-110.7)	0.3176	102.5 (89.0-119.5)	101.5 (93.0-105.0)	0.5029
RV/TLC	0.52 (0.44-0.59)	0.48 (0.40-0.54)	0.0520	0.48 (0.41-0.55)	0.48 (0.45-0.53)	0.7533
Impulse oscillometry						
R_5 [kPa/(L/s)]	0.55 (0.42-0.70)	0.49 (0.41-0.61)	0.7863	0.55 (0.37-0.67)	0.56 (0.42-0.64)	0.6202
R_5 (% of predicted)	168.6 (125.8-194.2)	156.9 (124.6-186.0)	0.8401	159.1 (133.5-202.0)	162.9 (136.5-195.9)	0.6379
R_5-R_{20} [kPa/(L/s)]	0.18 (0.10-0.34)	0.17 (0.09-0.26)	0.6071	0.22 (0.12-0.26)	0.18 (0.13-0.25)	0.9893
R_5-R_{20} (% of predicted)	288.9 (171.0-394.6)	218.4 (151.5-317.6)	0.1579	244.8 (173.4-366.1)	243.8 (186.9-336.1)	0.6381
F_{res} (Hz)	20.48 (14.49-26.52)	19.54 (15.63-22.64)	0.4576	19.65 (17.42-22.28)	20.85 (17.98-23.78)	0.2692
F_{res} (% of predicted)	136.3 (113.9-184.3)	132.2 (108.4-170.3)	0.5272	132.2 (120.9-162.2)	139.1 (123.7-162.9)	0.5341
X_5 [kPa/(L/s)]	-0.24 (-0.54 - -0.18)	-0.13 (-0.29 - -0.05)	**0.0152**	-0.27 (-0.42 - -0.13)	-0.35 (-0.46 - -0.18)	0.2427
X_5 (% of predicted)	252.5 (183.0-372.1)	208.9 (71.8-276.5)	0.1662	227.1 (112.9-313.7)	256.1 (146.9-359.4)	0.8089

AX (kPa/L)	1.73 (0.81-4.32)	1.73 (0.82-3.18)	0.5390	2.12 (1.12-3.18)	2.19 (1.30-3.30)	0.6204
AX (% of predicted)	447.4 (263.9-899.9)	467.5 (276.8-678.2)	0.4432	408.4 (209.2-583.8)	421.4 (262.8-627.8)	0.7901

Twenty-five patients received biologics treatment for severe asthma and completed 12 months follow-up, including omalizumab (n=17, 68%), mepolizumab (n=7, 28%), and benralizumab (n=1, 4%). BMI, body mass index; ACT, asthma control test; FeNO, fractional exhaled nitric oxide; PEFR: peak expiratory flow rate; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; $FEF_{25-75\%}$: forced expiratory flow between 25 and 75% of forced vital capacity; BDR (+), a positive bronchodilator response, defined as an increase in FEV_1 or FVC for more than 12% and 200 mL from the baseline in response to a short-acting beta-2 agonist; RV/TLC, the ratio of residual volume to total lung capacity ratio; R_5, resistance in 5 Hz; R_{20}, resistance in 20 Hz; F_{res}, resonant frequency; X_5, reactance in 5 Hz; AX, area under reactance curve between 5 Hz and resonant frequency; data are shown as number (%) for categorical variables and median (interquartile range, IQR) for non-normally distributed variables. *p* values were calculated from a comparison between patients at baseline and at 12-month follow-up by the McNemar's test for categorical variables and the Wilcoxon signed-rank test for continuous variables, and the values <0.05 were considered statistically significant. * indicates that *p* values were generated from a comparison between patients with and without biologics treatment.