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Small airway dysfunction and associated clinical characteristics in severe asthma under omalizumab and mepolizumab treatment

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Abstract

Background: Small airway dysfunction (SAD) plays a critical role in the pathophysiology of asthma.

Objective: This study aimed to evaluate the frequency of SAD in patients with severe asthma, and to assess its association with asthma control.

Methods: A total of 84 severe asthma patients were included in the study. Patients were classified into phenotypes according to the presence of allergy, fungal sensitization, obesity, blood eosinophil counts and frequency of asthma exacerbations. Impulse oscillometry (IOS) and spirometry were performed for all patients.

Results: Sixty-nine patients (83.1%) had allergic, 75 (91.5%) eosinophilic, 43 (51.2%) obese asthma, 25 (31.6%) asthma with fungal sensitization, and 24 (28.6%) were frequent-exacerbators. The detection rates of SAD by IOS and spirometry in the overall group, allergic asthma, eosinophilic asthma, obese asthma, asthma with frequent-exacerbations and asthma with fungal sensitization groups were as follows, respectively: 85.7% and 84.0%; 87.0% and 86.4%; 89.3% and 86.1%; 86.0% and 82.5%; 87.5% and 85.7%; 92.0% and 87.0%. The rate of SAD detected by IOS was significantly higher in the eosinophilic group compared with the non-eosinophilic group (89.3% vs. 57.1%, $p = 0.047$). SAD was detected in 92.5% of patients with controlled and 100% of those with uncontrolled asthma ($p = 0.292$). Area of reactance (A_X) and resonant frequency (F_{res}) were lower in the controlled group ($p = 0.044$, 0.005, respectively).

Conclusion: The frequency of SAD is significantly higher in eosinophilic asthma compared with non-eosinophilic asthma, while similar across allergic, obese, fungal sensitization and frequent-exacerbator phenotypes. Higher A_X and F_{res} values may be potentially indicative of uncontrolled asthma.

Key words: Asthma phenotypes; impulse oscillometry; mepolizumab; omalizumab; severe asthma; small airway dysfunction, spirometry.

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Abbreviations:

ABPA	Allergic bronchopulmonary aspergillosis
ACT	Asthma control test
A_X	Area of reactance
COPD	Chronic obstructive pulmonary disease
FEF	Forced expiratory flow
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in 1 second
FEV_3/FEV_6	Forced expiratory volume in 3 second/ Forced expiratory volume in 6 second
F_{res}	Resonant frequency
FVC	Forced vital capacity

Abbreviations (Continued):

ICS	Inhaled corticosteroids
IgE	Immunoglobulin E
Il-5	Interleukin 5
IOS	Impulse oscillometry
LABA	Long-acting beta2-agonist
LAMA	Long-acting muscarinic antagonists
$MMEF_{25–75}$	Maximal mid-expiratory flow between 25% and 75% of forced vital capacity
R_5	Resistance at 5 Hz
R_5-R_{20}	The difference between R_5 and R_{20}
R_{20}	Resistance at 20 Hz
SAD	Small airway dysfunction
SAFS	Severe asthma with fungal sensitization
SAwoFS	Severe asthma without fungal sensitization
X_5	Reactance at 5 Hz

Introduction

Asthma is a common, heterogeneous disease characterized by various clinical phenotypes and defined by distinct underlying mechanisms. The clinical features, natural course, pathophysiological mechanisms, and treatment response differ across asthma phenotypes.[1] From both a social and economic standpoint, asthma represents a significant burden and cause of morbidity for patients, their families, and healthcare systems.[2] Globally, asthma affects approximately 300 million individuals.[3]

Severe asthma is defined as asthma that remains uncontrolled despite high-dose inhaled corticosteroids (ICS)/long-acting beta 2-agonist (LABA), or that can only be controlled with such therapy and loses control when treatment is stepped down, after confirming the diagnosis of asthma and addressing modifiable factors that affect control (e.g. treatment adherence, inhaler technique, and comorbidities).[3] Severe asthma patients represent 3.7–7% of all asthma cases.[4,5] Despite being a small subset, they account for frequent clinic visits, high medication burden, and an overall per-patient cost that exceeds that of many other chronic illnesses.

The grouping of observable clinical characteristics that arise from gene–environment interactions constitute asthma phenotypes.[6,7] Pathological or molecular characteristics that detail phenotypic differences and reflect the nature of airway inflammation are referred to as endotypes.[7–9] Accurate identification of the asthma phenotype is a key element in guiding optimal treatment. In severe asthma in particular, phenotype classification based on biomarkers has well-established clinical utility due to the need for personalized therapeutic approaches.[10]

SAD in asthma is characterized by pathological abnormalities of the peripheral bronchioles, frequently observed across all disease severities and associated with asthma severity.[11] The prevalence of SAD in asthma patients ranges between 50% and 60%.[12] Multiple studies and systematic reviews have demonstrated that SAD is associated with greater bronchial hyperresponsiveness, poorer asthma control and more frequent exacerbations.[13–17] Several diagnostic tools are available to assess small airways, the most widely used being the measurement of maximal mid-expiratory flow between 25% and 75% of forced vital capacity ($MMEF_{25–75}$) via spirometry. However, there is no consensus regarding the reliability of $MMEF_{25–75}$ in evaluating small airway function.[18,19] IOS is a non-effort-dependent pulmonary function test based on the forced oscillation technique.[20] This method involves superimposing sound waves of multiple frequencies on normal tidal breathing. Resistance at 5 Hz (R_5) reflects total airway resistance, while resistance at 20 Hz (R_{20}) reflects central airway resistance. Reactance at 5 Hz (X_5) reflects the elastic properties (compliance) of the respiratory system. The R_5–R_{20} difference is considered sensitive to heterogeneous narrowing in the peripheral airways and indicative of SAD. IOS has potential applications in individuals who have difficulty performing spirometry.[21] Some studies have shown that IOS may be more useful than spirometry for identifying uncontrolled asthma and predicting loss of control or exacerbations, particularly in pediatric populations.[22–25] IOS has been reported to correlate more closely with clinical symptoms in asthma compared with spirometry, likely because it detects subtle changes in the airways earlier.[26] In a recent large multicenter study, asthma patients exhibited higher R_5 values compared with patients with COPD or bronchiectasis at the same FEV_1 level, attributed to greater central airway resistance (R_{20}).[27] Another study in pediatric and adolescent asthma patients compared spirometry and IOS parameters between controlled and uncontrolled asthma groups, finding no significant differences in either test between the two groups.[28] Although the respiratory oscillometry technique is promising for asthma monitoring, its use in clinical practice outside of research settings is not yet widespread.

Given the limited literature comparing asthma phenotypes in terms of small airway dysfunction (SAD), this study aimed to investigate the prevalence of SAD in severe asthma and compare its frequency across different asthma phenotypes, thereby contributing to the understanding of small airway involvement in distinct asthma phenotypes.

Methods

Patient selection and study design

The study included patients with a diagnosis of severe asthma who applied to our tertiary allergy clinic between April 2023 and March 2024 consecutively. We used the GINA 2024 guideline for the diagnosis and classification of severe asthma.[3] Based on past clinical and laboratory findings, patients were classified into asthma phenotypes: those with allergen sensitization consistent with clinical findings, as determined by skin prick testing and/or serum-specific immunoglobulin E (IgE) measurement, were categorized as having the allergic phenotype; those whose highest eosinophil count within the previous year was ≥ 150/mm^3 or who were receiving mepolizumab were categorized as having the eosinophilic phenotype; those with a body mass index ≥ 30 kg/m^2 were categorized as having obese asthma; those who had experienced two or more exacerbations within the previous year requiring systemic corticosteroid use for ≥ 3 days were categorized as having the frequent-exacerbation phenotype; and those who tested positive for Aspergillus fumigatus and/or Cladosporium herbarum and/or Alternaria alternata based on skin prick tests and/or specific IgE measurements were categorized as having severe asthma

with fungal sensitization (SAFS). All patients underwent the Asthma Control Test (ACT), laboratory assessments, spirometry and IOS. According to ACT scores, patients with a score ≥ 20 were considered controlled, whereas those with a score < 20 were considered uncontrolled. Written informed consent was obtained from all participants, and the study was approved by the institutional ethics committee (approval date and number: 29.03.2023, 2023/19-15).

Spirometry and IOS

IOS were performed for all patients using the device available at our center (Jaeger® Vyntus IOS™, CareFusion, Germany). Measurements were obtained in a seated upright position, nostrils occluded, hands gently supporting the cheeks and during tidal breathing.[21] In accordance with the manufacturer's recommendations, three measurements of at least 30 seconds each were performed. The following parameters were recorded: R_5 (%), R_{20} (%), the difference between R_5 and R_{20} (R_5–R_{20}) (kPa/L/s) , X_5 (%), resonant frequency (F_{res})(Hz) and area of reactance (A_X)(kPa/L). Five minutes after IOS measurement, spirometry was performed using the same device in accordance with international guidelines.[29] SAD was defined as $MMEF_{25–75}$ ≤ 65% predicted in spirometry or R_5–R_{20} > 0.07 kPa/L/s in IOS.[13,31] The measurements were performed while the patients were already receiving biological therapy.

Statistical analysis

Statistical analyses were performed using SPSS software. Categorical variables were expressed as frequencies, continuous variables were expressed as mean ± standard deviation and median (minimum–maximum). The normality of distribution for continuous variables was assessed both visually (histograms and probability plots) and analytically (Kolmogorov–Smirnov/Shapiro–Wilk tests). Descriptive statistics were presented as mean and standard deviation for normally distributed variables and as median and minimum–maximum for non-normally distributed variables. Comparisons between groups were performed using the Chi-square test, Fisher's exact test, Student's *t*-test or Mann–Whitney U test, as appropriate. A *p*-value < 0.05 was considered statistically significant in all analyses.

Results

Demographic and clinical characteristics of the study population

A total of 84 patients with a diagnosis of severe asthma were included in the study. The mean (minimum–maximum) age of the patients was 54.4 (22–74) years, and 64 (76.2%) were female. Sixty-nine patients (83.1%) had allergic asthma, 75 (91.5%) had eosinophilic, 43 (51.2%) had obese asthma, 25 (31.6%) had SAFS and 24 (28.6%) had frequent-exacerbations. All patients were receiving biological therapy for severe asthma: 52 (61.9%) were on omalizumab and 32 (38.1%) were on mepolizumab. The percentages of omalizumab and mepolizumab use in different asthma phenotypes were as follows: 73.9% vs. 26.1% in patients with the allergic phenotype, 57.3% vs. 42.6% in eosinophilic phenotype, 69.7% vs. 30.2% in obese asthma phenotype, 70.3% vs. 29.6% in SAFS, and 56.0% vs. 44.0% in frequent exacerbation phenotype.

The mean age at asthma onset was 35.81 ± 12.84 years and the mean duration of asthma diagnosis was 18.10 ± 10.83 years. Age at asthma onset was significantly lower in the SAFS compared with the SAwoFS (31.64 ± 12.28 vs. 38.33 ± 12.84 years, $p = 0.032$). In the allergic phenotype, the duration of asthma was significantly longer than the non-allergic phenotype (19.42 ± 10.80 vs. 12.64 ± 8.92 years, $p = 0.031$). The demographic and clinical characteristics of the patients are presented in **Table 1**.

Prevalence of SAD and asthma control

According to IOS, the prevalence of SAD in the entire cohort was 85.7% and according to spirometry, it was 83.9%. When IOS and spirometry results were evaluated together, the prevalence of SAD was 95.2% (**Table 4**). SAD was detected in 92.5% of patients with controlled asthma and in 100% of those with uncontrolled asthma ($p = 0.292$). The prevalence of SAD detected by IOS was significantly higher in the eosinophilic group compared with the non-eosinophilic group (89.3% vs. 57.1%, $p = 0.047$) (**Table 2**). Based on ACT scores, the proportion of patients with controlled asthma (ACT ≥ 20) was 63.1% (n = 53). The rate of controlled asthma was significantly higher in the non-eosinophilic phenotype compared with the eosinophilic phenotype (100% vs. 61.3%, $p = 0.048$) (**Table 1**). The prevalence of SAD was similar among patients receiving omalizumab and mepolizumab ($p > 0.05$) (**Table 5**).

The A_X was significantly lower in the controlled group compared with the uncontrolled group [1.42 (0.03–7.15) vs. 2.55 (0.03–6.51), $p = 0.044$]. Similarly, the F_{res} parameter was lower in the controlled group compared with the uncontrolled group (20.41 vs. 27.20, $p = 0.005$). No other IOS parameters differed significantly between the two groups ($p > 0.05$) (**Table 3**).

IOS and spirometry data according to asthma phenotypes

No significant differences were found between different asthma phenotypes in terms of R_5 percentage, R_{20} percentage, R_5–R_{20}, X_5 percentage, A_X and F_{res} values ($p > 0.05$) (**Table 2**). In patients with the allergic asthma phenotype, FEV_1 (% predicted) and FVC (% predicted) were significantly lower compared with those with the non-allergic phenotype [(68.31 ± 23.46) vs. (81.92 ± 16.05), $p = 0.042$; (82.28 ± 19.49) vs. (98.00 ± 13.91), $p = 0.005$, respectively]. In the non-obese group, the FEV_1/FVC ratio was lower than in the obese phenotype [(64.87 ± 13.30) vs. (71.33 ± 8.57), $p = 0.009$]. Comparison of phenotypes in terms of other spirometry and IOS parameters is provided in **Table 2**.

Table 1. Demographic and clinical characteristics of patients according to phenotypes.*

Patient characteristics	All patients (n = 84)	Eosinophilic asthma (n = 75)	Non-eosinophilic asthma (n = 7)	*P* value	Allergic asthma (n = 69)	Non-allergic asthma (n = 14)	*P* value	Obese asthma (n = 43)	Non-obese asthma (n = 41)	*P* value	Frequent exacerbation asthma (n = 24)	Non-frequent exacerbation asthma (n = 60)	*P* value	SAFS (n = 25)	SAwoFS (n = 54)	*P* value
Sex (female), n(%)	64(76.2)	55 (73.3)	7 (100)	0.186	54 (78.3)	9 (64.3)	0.309	37 (86.0)	27 (65.9)	0.030	21 (87.5)	43 (71.7)	0.124	16 (64.0)	41 (75.9)	0.994
Age (years), (mean ± SD)	54.39 **(±11.00)**	54.05 **(±11.13)**	59.00 **(±9.18)**	0.258	55.33 **(±10.38)**	50.00 **(±13.53)**	0.100	57.37 **(±9.77)**	51.27 **(±11.47)**	0.010	52.25 **(±12.26)**	55.25 **(±10.44)**	0.262	52.88 **(±9.96)**	54.48 **(±11.56)**	0.552
BMI (kg/m^2), (mean ± SD)	30.13 **(±5.98)**	29.84 **(±6.13)**	32.42 **(±4.61)**	0.281	30.68 **(±6.02)**	27.77 **(±5.40)**	0.098	34.83 **(±4.18)**	25.20 **(±2.68)**	0.000	31.06 **(±6.93)**	29.76 **(±5.58)**	0.371	28.60 **(±6.14)**	30.48 **(±5.85)**	0.196
Smoking status, n(%)																
Current smoker	6 (7.1)	6 (8.0)	0 (0)		4 (5.8)	2 (14.3)		2 (4.7)	4 (9.8)		0 (0)	6 (10.0)		2 (8.0)	3 (5.6)	
Former smoker	26 (30.9)	26 (34.7)	0 (0)		21 (30.4)	5 (35.7)		10 (23.2)	16 (39.0)		7 (29.2)	19 (31.7)		7 (28.0)	18 (33.3)	
Never smoker	52 (61.9)	43 (57.3)	7 (100)		44 (63.8)	7 (50.0)		31 (72.1)	21 (51.2)		17 (70.8)	35 (58.3)		16 (64.0)	33 (61.1)	
Smoking history (pack-years), median (min-max)	11.50 (1-60)	11.00 (1-60)	-	-	14.00 (1-60)	9.00 (3-20)	0.789	15.00 (1-30)	10 (2-60)	0.209	10.00 (6-25)	15.00 (1-60)	0.420	10.00 (2-34)	15.00 (1-60)	0.824
Asthma duration (years), (mean ± SD)	18.10 (±10.83)	18.39 (±10.96)	18.29 (±9.41)	0.981	19.42 (±10.80)	12.64 (±8.92)	**0.031**	18.81 (±11.31)	17.34 (±10.38)	0.537	16.79 (±11.15)	18.62 (±10.75)	0.489	21.24 (±11.97)	16.15 (±9.92)	0.051
Age at asthma onset (years), (mean ± SD)	35.81 (±12.81)	35.63 (±12.69)	40.71 (±14.93)	0.320	35.87 (±12.76)	37.36 (±13.53)	0.695	38.49 (±13.11)	33.93 (±12.21)	0.103	35.46 (±11.96)	36.58 (±13.22)	0.719	31.64 (±12.28)	38.33 (±12.84)	**0.032**
Family history of asthma, n(%)	37 (44.0)	34 (45.3)	2 (28.6)	0.458	29 (42.0)	8 (57.1)	0.300	18 (41.9)	19 (46.3)	0.679	12 (50.0)	25 (41.7)	0.487	10 (40.0)	25 (46.3)	0.600
Associated comorbid conditions, n(%)	60 (71.4)	57 (76.0)	3 (42.8)	0.079	49 (71.0)	10 (71.4)	1.000	27 (62.8)	33 (80.5)	0.073	20 (83.3)	40 (66.7)	0.127	20 (80.0)	38 (70.4)	0.368
Allergic rhinitis	44 (52.4)	41 (54.7)	3 (42.8)	0.699	43 (62.3)	0 (0)	**< 0.001**	22 (51.2)	22 (53.7)	0.819	17 (70.8)	27 (45.0)	**0.032**	17 (68.0)	27 (50.0)	0.134
Urticaria/Angioedema	2 (2.4)	2 (2.7)	0 (0)	1.000	2 (2.9)	0 (0)	1.000	2 (4.7)	0 (0)	0.494	0 (0)	2 (3.3)	1.000	0 (0)	2 (3.7)	1.000
Anaphylaxis	1 (1.2)	1 (1.3)	0 (0)	1.000	1 (1.2)	0 (0)	1.000	1 (1.2)	0 (0)	1.000	0 (0)	1 (1.2)	1.000	0 (0)	1 (1.3)	1.000
ABPA	2 (2.4)	2 (2.7)	0 (0)	1.000	2 (2.9)	0 (0)	1.000	1 (2.3)	1 (2.4)	1.000	1 (4.2)	1 (2.7)	0.492	2 (8.0)	0 (0)	0.097
NSAID intolerance	6 (7.1)	6 (8.0)	0 (0)	1.000	5 (7.2)	1 (7.1)	1.000	2 (4.7)	4 (9.8)	0.427	0 (0)	6 (10.0)	0.176	2 (8.0)	3 (5.6)	0.649
Nasal polyps	12 (14.3)	12 (16.0)	0 (0)	0.586	6 (8.7)	6 (42.9)	**0.004**	1 (2.3)	11 (26.8)	**0.001**	2 (8.3)	10 (16.7)	0.495	4 (16.0)	8 (14.8)	1.000
Other comorbidities, n(%)	51 (60.7)	44 (58.7)	5 (71.4)	0.696	43 (62.3)	8 (57.1)	0.717	33 (76.7)	18 (43.9)	**0.002**	15 (62.5)	36 (60.0)	0.832	13 (52.0)	33 (61.1)	0.445
Atopy, n(%)	69 (83.1)	60 (81.1)	7 (100)	0.345	69 (100)	0 (0)	**< 0.001**	38 (88.4)	31 (77.5)	0.186	19 (82.6)	50 (83.3)	1.000	25 (100)	40 (75.5)	**0.007**
Pollen sensitization	26 (32.1)	25 (34.2)	1 (14.3)	0.418	26 (38.8)	0 (0)	**0.004**	12 (29.3)	14 (35.0)	0.581	6 (26.1)	20 (34.5)	0.466	10 (40.0)	16 (30.2)	0.391
House dust mite sensitization	44 (52.4)	38 (52.1)	5 (71.4)	0.442	44 (64.7)	0 (0)	**< 0.001**	24 (57.1)	20 (50.0)	0.517	14 (60.9)	30 (50.8)	0.414	8 (32.0)	34 (64.2)	**0.008**
Mold sensitization	25 (31.6)	24 (32.4)	1 (14.3)	0.427	25 (37.9)	0 (0)	**0.007**	10 (25.0)	15 (38.5)	0.232	6 (27.3)	19 (33.3)	0.788	25 (100)	0 (0)	**< 0.001**
Cat sensitization	4 (4.8)	4 (5.6)	0 (0)	1.000	4 (6.1)	0 (0)	1.000	1 (2.4)	3 (7.9)	0.347	0 (0)	4 (7.0)	0.572	2 (8.3)	2 (3.8)	0.587
Dog sensitization	2 (2.4)	2 (2.8)	0 (0)	1.000	2 (2.8)	0 (0)	1.000	1 (2.4)	1 (2.6)	1.000	0 (0)	2 (3.5)	1.000	0 (0)	2 (3.8)	1.000
ACT score, median (min-max)	21 (5-25)	21 (5-25)	23 (20-25)	0.077	20 (8-25)	23 (20-25)	0.208	17 (8-25)	22 (11-25)	0.195	16 (8-23)	22 (14-25)	**< 0.001**	22 (8-25)	20 (14-25)	0.775
Controlled asthma (ACT ≥ 20), n (%)	53 (%63.1)	46 (%61.3)	7 (%100)	**0.048**	40 (%57.9)	12 (%85.7)	0.05	24 (%55.8)	29 (%70.7)	0.157	7 (%29.1)	46 (%76.6)	**< 0.001**	17 (%68.0)	35 (%64.8)	0.781
Blood eosinophil count (cells/µL), median (min-max)	400 (100-1650)	500 (100-1650)	100 (100-100)	**0.000**	435 (100-1200)	350 (200-500)	0.932	470 (160-900)	400 (100-1200)	0.321	665 (200-1200)	380 (100-1000)	0.325	400 (100-1000)	470 (160-1200)	0.765

Table 1. (Continued)

Patient characteristics	All patients (n = 84)	Eosinophilic asthma (n = 75)	Non-eosinophilic asthma (n = 7)	*P* value	Allergic asthma (n = 69)	Non-allergic asthma (n = 14)	*P* value	Obese asthma (n = 43)	Non-obese asthma (n = 41)	*P* value	Frequent exacerbation asthma (n = 24)	Non-frequent exacerbation asthma (n = 60)	*P* value	SAFS (n = 25)	SAwoFS (n = 54)	*P* value
Total IgE (kU/L), median (min-max)	227 (16-3751)	242 (16-3300)	54 (32-317)	**0.009**	240 (26-3300)	26 (21-337)	0.639	127 (78-1030)	255 (21-3300)	0.336	99.50 (21-900)	268 (25-3300)	0.235	255 (26-3300)	127 (21-1030)	0.337
Frequent asthma exacerbations, n(%)	24 (28.6)	22 (29.3)	1 (14.3)	0.677	19 (27.5)	4 (28.6)	1.000	13 (30.2)	11 (26.8)	0.730	24 (100)	0 (0)	**0.000**	6 (22.2)	17 (32.1)	0.357
ICS dosage																
High	24 (28.6)	23 (30.7)	1 (14.3)		19 (27.5)	4 (28.6)		13 (30.2)	11 (26.8)		15 (62.5)	9 (15)		7 (28.0)	15 (27.8)	
Medium	44 (52.4)	40 (53.3)	3 (42.9)	0.197	35 (50.7)	9 (64.3)	0.429	20 (46.5)	24 (58.5)	0.476	6 (25)	38 (63.3)	**0.000**	10 (40.0)	31 (57.4)	0.175
Low	16 (19.0)	12 (16.0)	3 (42.9)		15 (21.7)	1 (7.1)		10 (23.3)	6 (14.6)		3 (12.5)	13 (21.7)		8 (32.0)	8 (14.8)	

BMI: Body Mass Index; ABPA: Allergic bronchopulmonary aspergillosis; NSAID: Non-steroidal anti-inflammatory drug; ACT: Asthma Control Test;IgE: Immunoglobulin E, ICS: Inhaled corticosteroid, SAFS: Severe asthma with fungal sensitization, SAwoFS: Severe asthma without fungal sensitization.
*Since eosinophil data were missing for 2 patients, atopy data for 1 patient, and fungal sensitization data for 5 patients, the denominator values for these groups were 82, 83, and 79, respectively, and the group analyses were conducted based on these denominators.

Table 2. Comparison of asthma phenotypes in terms of IOS parameters and prevalence of SAD.

	All patients (n = 84)	Eosinophilic asthma (n = 75)	Non-eosinophilic asthma (n = 7)	*P* value	Allergic asthma (n = 69)	Non-allergic asthma (n = 14)	*P* value	Obese asthma (n = 43)	Non-obese asthma (n = 41)	*P* value	Frequent exacerbation asthma (n = 24)	Non- frequent exacerbation asthma (n = 60)	*P* value	SAFS (n = 25)	SAwoFS (n = 54)	*P* value
R_5 (%), median (min-max)	137 (25-387)	144 (25-276)	140 (59-387)	0.934	140 (25-387)	148 (81-223)	0.733	144 (39-387)	125.5 (25-258)	0.147	130 (25-213)	141.5 (39-387)	0.147	130 (39-387)	143 (25-258)	0.620
R_{20} (%), mean ± SD	102.12 (±29.35)	101.27 (±28.61)	112.14 (±34.40)	0.347	99.49 (±28.61)	110.93 (±33.23)	0.188	99.29 (±28.48)	103.33 (±30.38)	0.533	99.25 (±35.42)	102.20 (±26.85)	0.680	93.36 (±20.44)	104.57 (±31.75)	0.064
R_5-R_{20} (kPa/L/s), median (min-max)	0.190 (0.00-1.16)	0.190 (0.00-0.81)	0.140 (0.04-1.16)	0.618	0.200 (0.02-1.16)	0.175 (0.00-0.37)	0.231	0.210 (0.02-1.16)	0.155 (0.00-0.48)	0.077	0.160 (0.02-0.48)	0.200 (0.00-1.16)	0.077	0.170 (0.03-1.16)	0.195 (0.00-0.59)	0.912
X_5 (%), median (min-max)	231 (-10413-3551)	261 (-10413-3551)	208 (41-980)	0.778	261 (-10413-3551)	167 (-534-2376)	0.285	304 (-3957-3001)	211 (-10413-3551)	0.182	244 (-3957-2376)	240.5 (-10413-3551)	0.182	304 (-10413-2222)	221.5 (-3957-3551)	0.808
A_X (kPa/L), median (min-max)	1.74 (0.03-7.15)	1.89 (0.03-6.51)	1.39 (0.19-7.15)	0.648	1.87 (0.03-7.15)	1.63 (0.03-3.80)	0.359	2.05 (0.03-7.15)	1.40 (0.03-5.32)	0.093	1.74 (0.09-5.49)	1.71 (0.03-7.15)	0.093	1.68 (0.03-7.15)	1.80 (0.03-4.32)	0.895
F_{res} (Hz), median (min-max)	21.30 (7.39-39.50)	22.06 (7.39-39.50)	21.24 (11.72-29.94)	0.366	21.72 (11.29-39.50)	21.68 (7.39-32.64)	0.913	23.06 (11.29-36.92)	19.84 (7.39-33.98)	0.075	22.06 (16.46-36.92)	21.27 (7.39-34.33)	0.075	19.37 (11.29-36.92)	22.35 (7.39-35.59)	0.373
SAD (by IOS), n(%)	72 (%85.7)	67 (%89.3)	4 (%57.1)	**0.047**	60 (%87.0)	11 (%78.6)	0.417	37 (%86.0)	35 (%85.4)	0.929	21 (%87.5)	51 (%85.0)	1.000	23 (%92.0)	46 (%85.2)	0.490
SAD (by Spirometry), n(%)	68 (%83.9)	62 (%86.1)	5 (%71.4)	0.287	57 (%86.4)	11 (% 78.6)	0.432	33 (%82.5)	35 (%85.4)	0.725	18 (%85.7)	50 (%83.3)	1.000	20 (%87)	44 (%83)	1.000
FEV_1 (%), mean ± SD	71.09 **(±23.17)**	69.77 **(±23.07)**	76.14 **(±21.64)**	0.485	68.31 **(±23.46)**	81.92 **(±16.05)**	**0.042**	72.11 **(±23.45)**	70.02 **(±23.12)**	0.682	69.75 **(±25.74)**	71.63 **(±22.27)**	0.739	64.20 **(±24.23)**	73.75 **(±22.36)**	0.088
FVC (%), mean ± SD	85.39 **(±19.84)**	84.78 **(±20.36)**	86.42 **(±13.91)**	0.836	82.28 **(±19.49)**	98.00 **(±13.91)**	**0.005**	82.55 **(±20.57)**	88.36 **(±18.83)**	0.182	82.04 **(±23.79)**	86.73 **(±18.07)**	0.390	79.52 **(±21.84)**	88.53 **(±18.73)**	0.063
FEV_1/FVC, mean ± SD	68.18 **(±11.53)**	67.37 **(±11.47)**	72.47 **(±10.12)**	0.260	67.81 **(±11.82)**	69.42 **(±10.55)**	0.638	71.33 **(±8.57)**	64.87 **(±13.30)**	**0.009**	69.73 **(±9.71)**	67.56 **(±12.21)**	0.439	66.35 **(±12.82)**	68.30 **(±10.93)**	0.487
$MMEF_{25/75}$ (%), median (min-max)	35.00 (6-121)	34.00 (6-121)	42.00 (18-92)	0.407	33.00 (6-121)	46.00 (18-90)	0.085	35.00 (13-101)	34.00 (6-121)	0.438	34.50 (11-76)	34:50 (6-121)	0.889	21.00 (6-121)	36.50 (8-101)	0.067

R_5: Resistance at 5 Hz, R_{20}: Resistance at 20 Hz, X_5: Reactance at 5 Hz, A_X: Area of reactance, F_{res}: Resonant frequency, IOS: Impulse oscillometry, FEV_1: Forced expiratory volume in 1 second, FVC: Forced vital capacity, $MMEF_{25/75}$: Maximal mid-expiratory flow (25–75%), SAD: Small airway dysfunction, SAFS: Severe asthma with fungal sensitization, SAwoFS: Severe asthma without fungal sensitization

Table 3. Comparison of IOS parameters between controlled and uncontrolled asthma according to ACT.

Variable	Controlled asthma (n = 53)	Uncontrolled asthma (n = 31)	*P* value
R_5 (%), median (min-max)	124 (59-387)	167 (25-276)	0.059
R_{20} (%), mean ± SD	99.47 (±23.73)	104.58 (±37.31)	0.497
R_5-R_{20} (kPa/L/s), median (min-max)	0.170 (0.03-1.16)	0.230 (0.02-0.81)	0.070
X_5 (%), median (min-max)	220 (-10413-3001)	261 (-3957-3551)	0.321
A_X (kPa/L), median (min-max)	1.42 (0.03-7.15)	2.55 (0.03-6.51)	0.044
F_{res} (Hz), median (min-max)	20.41 (7.39-36.92)	27.20 (11.29-39.50)	0.005

R_5: Resistance at 5 Hz, R_{20}: Resistance at 20 Hz, X_5: Reactance at 5 Hz, A_X: Area of reactance, F_{res}: Resonant frequency, ACT: Asthma Control Test.

Table 4. The prevalence of SAD by spirometry and IOS.

Diagnostic method	n*	SAD , n (%)
Spirometry	81	68 (83.9)
IOS	84	72 (85.7)
IOS + spirometry	84	80 (95.2)

IOS: Impulse oscillometry, SAD: Small airway disease
* The percentages were calculated based on the available (complete) data for the relevant method.

Table 5. Comparison of SAD prevalence between treatment groups according to assessment methods.

Diagnostic method	Omalizumab (n = 52)	Mepolizumab (n = 32)	*p* value
Spirometry*	43/50 (86%)	25/31 (80,6%)	0.547
IOS	44/52 (84.6%)	28/32 (87.5%)	1.000
IOS + spirometry	50/52 (96.2%)	30/32 (93.8%)	0.633

SAD: Small airway disease
*Due to missing data, the spirometry analysis included 50 patients in omalizumab group and 31 in mepolizumab group.

Table 6. Univariable analysis of potential risk factors for SAD.

Potential risk factors	Odds ratio (OR)	95% Confidence Interval (CI)	*P*-value
Sex, female (ref: male)	1.070	0.105-10.901	0.954
Age	0.935	0.836-1.046	0.243
Asthma duration	1.010	0.919-1.111	0.835
Eosinophil count	1.005	0.998-1.012	0.178
Total IgE level	0.999	0.998-1.000	0.062
Smoking pack-years	0.988	0.894-1.091	0.805
Atopy, yes (ref: no)	0.179	0.023-1.397	0.101

SAD: Small airway disease, Ref: Reference

Risk factors for SAD

Univariate logistic regression analysis was performed to identify demographic and clinical risk factors for the development of SAD among patients with and without SAD. As a result of the analysis, it was determined that none of the demographic or clinical parameters examined (patient age, sex, duration of asthma, eosinophil count, total IgE level, pack-years of smoking, presence of atopy) showed a statistically significant association with the presence of SAD. Since none of the independent variables reached the threshold for statistical significance during the univariate analysis phase, a multivariate logistic regression model was not constructed. The crude odds ratios (OR), confidence intervals, and *p*-values for all parameters examined are summarized in **Table 6**.

Discussion

The prevalence of SAD was 85.7% according to IOS, and 83.9% according to spirometry in severe asthma patients on biological treatment in our study. When IOS and spirometry results were evaluated together, the prevalence of SAD was found to be 95.2%. In our study, in an adult severe asthma population, the prevalence of SAD was 100% in patients with uncontrolled asthma, while it was also notably high (92.5%) in those with controlled asthma. In the study by Cottini et al., the prevalence of SAD in patients with asthma according to IOS was 54.1%, whereas according to spirometry it was 10.0%.[30] That study also found that IOS-defined SAD was associated with lower asthma control rates, more severe asthma exacerbations and higher ICS doses. In another study involving 400 adults with stable asthma, SAD was detected in 246 patients (62.0%).[15] In this group, the rate of well-controlled asthma was lower compared to those without SAD (34.0% vs. 92.0%). In a study conducted on patients with mild and moderate asthma, the prevalence of SAD was assessed using spirometry and IOS; the prevalence of SAD was found to be 41.0% according to IOS.[31] In another study, it was noted that IOS, particularly in children, could predict asthma diagnosis and control more effectively than spirometry and could offer potential for early intervention.[32] The much higher prevalence of SAD in our study compared to others can be explained by the fact that all patients in our study had severe asthma. In our study, high rates of SAD were detected with both spirometry and IOS, and the combined use of the two methods further increased the detection rate of SAD. IOS and spirometry are complementary and could be used together to better understand and manage different aspects of asthma.

In our study, the SAD prevalence was higher in the eosinophilic group than in the non-eosinophilic group (89.3% [67/75] vs. 57.1% [4/7]; absolute difference 32.2%, 95%CI 3.7–64.7%). However, this comparison should be interpreted cautiously, as the evidence is limited due to the small number of patients in the non-eosinophilic group. Few studies have evaluated oscillometric parameters across severe asthma phenotypes, and data remain limited. In one study, asthma patients were classified into four inflammatory phenotypes based on the type and number of cells in induced sputum (eosinophilic, neutrophilic, mixed granulocytic and paucigranulocytic) and these phenotypes were compared

in terms of asthma severity, symptom control, exacerbation frequency and lung function.[37] It was found that patients with eosinophilic and mixed granulocytic phenotypes had a higher prevalence of SAD, poorer symptom control and more frequent severe exacerbations. Furthermore, eosinophilic asthma, compared with neutrophilic asthma, was associated with greater distal airway obstruction, increased ventilation heterogeneity and a greater tendency toward severe exacerbations. Similarly, in our study, we detected a higher prevalence of SAD in patients with the eosinophilic phenotype compared to those with the non-eosinophilic phenotype and the proportion of patients with controlled asthma was lower in the eosinophilic phenotype compared to the non-eosinophilic phenotype (61.3% vs. 100%). These findings suggest that eosinophilic inflammation may have a greater impact on the small airways, thereby making asthma control more difficult.

The relationship between asthma control and IOS parameters has been examined in some studies.[38,39] In our study, when patients with controlled and uncontrolled asthma according to ACT were compared in terms of IOS parameters, significant differences were found in A_X and F_{res} values, whereas no significant difference was observed in $R_5–R_{20}$. A_X and F_{res} values were higher in the uncontrolled severe asthma group. In the study by Palacios et al., no direct relationship was found between asthma control and IOS parameters.[39] In contrast, the study by Chaiwong et al. demonstrated that, in adult asthma patients with normal spirometry values, IOS parameters showed high efficacy in detecting poorly controlled asthma. In particular, the $R_5–R_{20}$ and A_X parameters were found to be highly effective in identifying poorly controlled asthma.[38] F_{res} is the point at which the capacitive reactance, related to thoracopulmonary elasticity and volume variability, equals the inertial reactance, which reflects the movement of the column of air within the respiratory tract. A F_{res} value higher than normal may indicate increased airway obstruction or stiffness, suggesting restricted airflow. A_X is the integral of reactance measured at low frequencies and reflects the elasticity of respiratory system and the degree of small airway obstruction. It provides information about the distal airways and its value increases as narrowing worsens.[40] The percentage change in A_X value following salbutamol inhalation was shown to be an effective method for predicting bronchodilator reversibility.[41] Taken together, these findings suggest that the A_X parameter, in particular, may be effective in identifying poorly controlled asthma regardless of whether spirometry results are normal.

In the literature, studies investigating the effects of biological agents on SAD have reported conflicting results.[33–36] In the study by Yılmaz et al., no significant change in FEF_{25-75} was observed in patients with severe eosinophilic asthma receiving mepolizumab,[33] whereas two other studies demonstrated improvement in this parameter with mepolizumab therapy.[34,35] In a study investigating the efficacy of omalizumab in severe asthma, despite a significant reduction in airway wall thickness with omalizumab treatment, no change was observed in the IOS $R_5–R_{20}$ value.[36] Since all patients in our study were already receiving biologic therapy at the time of evaluation, we were unable to assess whether there was any improvement in SAD before and after biologic therapy; however, the groups receiving omalizumab and mepolizumab were compared with each other, and no significant difference was found between the two groups in terms of SAD (**Table 5**).

Our study has some limitations. The absence of a control group and the relatively small sample size due to the single-center design are among the limitations of our study. The small number of patients in the non-eosinophilic phenotype group can also be considered a limitation. The high proportion of eosinophilic asthma in our study may be related to the fact that our study center is a tertiary allergy clinic, which tends to receive patient referrals predominantly with the eosinophilic phenotype. An important consideration is that all patients were evaluated while receiving biological therapy; this may have influenced the clinical and functional outcomes observed in this study. Future prospective longitudinal studies are needed to better define the natural history of small airway dysfunction (SAD) over time and to clarify the potential impact of biological therapies on SAD-related clinical, functional, and physiological outcomes.

Conclusion

The prevalence of SAD in patients with severe asthma is high and greater than the rates reported in the general asthma population. In the eosinophilic phenotype, the prevalence of SAD was significantly higher than in the non-eosinophilic phenotype. Regardless of phenotype, patients with uncontrolled asthma had higher A_X and F_{res} values on IOS compared to those with controlled asthma. SAD in asthma patients is associated with symptom control, and higher A_X and F_{res} values may be potentially indicative of uncontrolled asthma.

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