

Original Article

Small Airway Dysfunction in Asthma: Associations with Control and Quality of Life

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ABSTRACT

OBJECTIVE: Small airway dysfunction (SAD) is an important but frequently underrecognized component of asthma. This study aimed to determine the prevalence of SAD in asthma, as assessed by impulse oscillometry (IOS), and to evaluate its association with clinical outcomes.**MATERIAL AND METHODS:** This cross-sectional study, with a 12-month prospective follow-up, included adult patients with asthma. SAD was defined by IOS as $R5-R20 \geq 0.07$ kPa·s·L⁻¹. The asthma control test (ACT) and the asthma quality of life questionnaire (AQLQ) were administered. Exacerbations were prospectively recorded during the 12 months after enrollment. Patients were stratified according to the presence of SAD. Clinical and functional parameters were compared between groups.**RESULTS:** SAD was identified in 63 of 98 participants (64.3%). SAD prevalence differed significantly across the five Global Initiative for Asthma treatment steps ($P < 0.001$). Patients with SAD had significantly lower ACT scores ($P = 0.021$), poorer quality of life (AQLQ, $P = 0.002$), and more frequent exacerbations ($P < 0.001$) than those without SAD. In multivariable regression analyses, higher $R5-R20$ was independently associated with a lower AQLQ score ($\beta = -0.18$, 95% confidence interval -0.30 to -0.07 ; $P = 0.002$) and higher odds of being in a worse asthma control category (odds ratio 1.33, $P = 0.010$).**CONCLUSION:** SAD is common among patients with asthma and is associated with poorer asthma control, lower quality of life, and an increased exacerbation burden. Higher $R5-R20$ remained associated with poorer quality of life after adjustment for spirometry, whereas its association with asthma control was attenuated and became non-significant after adjustment for forced expiratory volume in the first second. These findings support further evaluation of IOS-defined SAD as a potentially clinically relevant trait in asthma.**KEYWORDS:** Asthma, small airway dysfunction, impulse oscillometry, asthma control, quality of life**Received:** 11.01.2026**Revision Requested:** 22.04.2026**Last Revision Received:** 13.09.2026**Accepted:** 21.09.2026**Epub:** 07.10.2026

INTRODUCTION

Asthma is a chronic inflammatory airway disease characterized by variable respiratory symptoms and airflow limitation. Spirometry is recommended as the primary tool for diagnosing and assessing airflow obstruction in routine clinical practice.¹ However, growing evidence indicates that conventional spirometric indices, particularly forced expiratory volume in the first second (FEV₁), may inadequately reflect symptom burden, asthma control, and health-related quality of life.^{2,3} Previous real-world and cohort studies have demonstrated a significant discordance between spirometric measurements and patient-reported outcomes, suggesting that clinically relevant disease may persist despite normal or near-normal spirometric values.²⁻⁴

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Small airways, defined as airways with an internal diameter of ≤ 2 mm, have gained increasing attention in asthma pathophysiology. Although they contribute minimally to total airway resistance under normal conditions, inflammation and structural remodeling of small airways may lead to ventilation heterogeneity, air trapping, and persistent symptoms.^{2,5,6} Histopathological studies have demonstrated inflammatory involvement of the distal airways even in patients with mild or well-controlled asthma, suggesting that small airway dysfunction (SAD) may be present despite apparently preserved lung function.^{7,8}

Spirometry remains the cornerstone of asthma diagnosis and follow-up; however, it has well-recognized limitations in detecting small airway involvement. Parameters such as forced expiratory flow between 25% and 75% of forced vital capacity (FEF_{25-75}) are often used as indirect markers of distal airway function, yet they are highly effort-dependent and show substantial variability. Importantly, spirometric indices may remain within normal ranges in patients with clinically relevant small airway impairment, limiting their ability to accurately reflect disease burden and symptom severity.^{9,10}

Impulse oscillometry (IOS) is a non-invasive, effort-independent technique that assesses respiratory system impedance during tidal breathing. By applying pressure oscillations at different frequencies, IOS allows the separate evaluation of central and peripheral airway mechanics. Parameters such as resistance at 5 Hz (R5), frequency-dependent resistance (R5–R20), reactance at 5 Hz (X5), and reactance area (AX) have been proposed as sensitive indicators of SAD. Several studies have suggested that IOS may detect distal airway abnormalities in asthmatic patients even when spirometric measurements are normal.^{11,12}

Although the clinical relevance of SAD in asthma has been increasingly recognized, data regarding its prevalence and association with asthma control and quality of life remain limited and inconsistent, particularly in real-world clinical settings. Moreover, studies integrating IOS-derived small

airway indices with validated patient-reported outcomes are scarce.^{2,13,14}

Therefore, the primary aim of this study was to determine the prevalence of SAD, assessed by IOS, in adult patients with asthma. The secondary aim was to investigate the relationship among IOS-defined SAD, asthma control, measured by the asthma control test (ACT), and health-related quality of life, assessed using the asthma quality of life questionnaire (AQLQ).

MATERIAL AND METHODS

Study Design and Setting

This study was designed as a cross-sectional investigation with a 12-month prospective follow-up. Patients with asthma were recruited from the Chest Diseases Clinic of Mersin University Hospital, Türkiye, between June 1, 2019, and November 1, 2019. All participants were intended to undergo a 12-month follow-up. Complete questionnaire and follow-up data were available for 74 participants, who constituted the longitudinal analysis cohort. Therefore, the overall follow-up period was completed on November 1, 2020. A convenience sampling method was employed. Individuals who met the inclusion criteria, did not meet any exclusion criteria, and provided written informed consent were enrolled. The study protocol was approved by the Mersin University Clinical Research Ethics Committee (decision no: 2019/199, dated: 08.05.2019) and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study was registered on ClinicalTrials.gov (NCT04375995).

Study Groups

A total of 105 participants with asthma were included. Patients were excluded if they had experienced an exacerbation within the past 4 weeks, had a coexisting pulmonary condition, had a history of lung surgery, had severe comorbidities (e.g., unstable cardiovascular disease, malignancy), or were unable to complete the required functional assessments.

Participants with a diagnosis of asthma for at least one year were included based on Global Initiative for Asthma (GINA) 2019 criteria, which require at least one of the following: a positive reversibility test (defined as an increase in FEV_1 $>12\%$ and >200 mL within 10–15 minutes after 400 μ g salbutamol via a metered-dose inhaler), a positive methacholine bronchial provocation test, peak expiratory flow variability $>10\%$, or documented reversibility after four weeks of maintenance therapy.

Procedures

Demographics and clinical characteristics were recorded. Spirometry and IOS were performed in all 105 participants. However, technically acceptable R5–R20 measurements suitable for SAD classification were available for 98 participants. Reliable R5–R20 values could not be obtained for seven participants because the IOS measurements did not meet technical acceptability criteria. In patients who agreed to complete the questionnaires and who provided complete responses ($n = 74$), asthma control and health-related quality of life were assessed using the ACT and the AQLQ. This subgroup was followed prospectively for 12 months to record exacerbation outcomes,

Main Points

- Small airway dysfunction (SAD) assessed by impulse oscillometry (IOS) is highly prevalent (64.3%) in adult patients with asthma and is also observed in patients with preserved spirometry.
- Higher R5–R20 was independently associated with reduced quality of life, with this association persisting after additional spirometric adjustment. Its association with asthma control was attenuated after adjustment for spirometric indices.
- Significant discordance exists between preserved spirometric indices and IOS-defined impairment, indicating that IOS-defined impairment may not be fully reflected in conventional spirometric indices.
- IOS may provide complementary information on small airway involvement beyond conventional spirometry, while the therapeutic implications of IOS-defined SAD require further investigation in prospective interventional studies.

including attacks requiring systemic corticosteroids, emergency department visits, unscheduled outpatient visits, and asthma-related hospitalizations. Patients who declined to complete the questionnaire or did not complete follow-up assessments were not included in the longitudinal analyses.

Pulmonary Function Tests

All participants underwent spirometry and IOS. Spirometry was performed using the MasterScreen™ PFT (CareFusion, Hoechst, Germany) in accordance with American Thoracic Society (ATS)/European Respiratory Society (ERS) 2019 standards.¹⁵ A post-bronchodilator test was conducted 15 minutes after administration of 400 µg salbutamol via a metered-dose inhaler. For comparative analyses, spirometric small-airway impairment was defined as $FEF_{25-75}\%$ <60%.¹⁶

IOS was performed using the Jaeger Vyntus IOS (CareFusion, Germany), with at least five valid trials per participant. Recorded parameters included R5, R20, X5, Fres, AX, and R5–R20.

SAD was primarily defined using an R5–R20 threshold of ≥ 0.07 kPa·s·L⁻¹, because this parameter reflects frequency-dependent resistance and is widely used as a clinically applicable IOS marker of peripheral airway dysfunction.^{4,17,18} Other IOS indices, including X5 and AX, were also evaluated as complementary parameters in descriptive and correlation analyses.

Fractional Exhaled Nitric Oxide (FeNO)

FeNO levels were measured in patients with asthma using the Bedfont NObreath® device (England) in accordance with ATS/ERS 2011 recommendations.¹⁹

Assessment of Asthma Control, Quality of Life, and Exacerbations

Asthma Control Test

Asthma symptom control was assessed using the validated Turkish version of the ACT.²⁰ The questionnaire was administered to the 74 participants who had complete responses. The ACT consists of five items, each scored on a 5-point Likert scale, yielding a total score ranging from 5 to 25. Based on the total score, asthma control was categorized as well controlled (20–25), partially controlled (16–19), or uncontrolled (5–15).¹

Asthma Quality of Life Questionnaire

Health-related quality of life was evaluated using the validated Turkish version of the AQLQ.²¹ The questionnaire includes 32 items across four domains: symptoms, activity limitation, emotional function, and environmental stimuli. Each item is scored on a 7-point scale ranging from 1 (severe impairment) to 7 (no impairment). In accordance with the conventional AQLQ scoring method, domain scores and the overall AQLQ score were calculated as means of the relevant item scores, yielding scores ranging from 1 to 7, with higher scores indicating better asthma-related quality of life.^{21,22}

Assessment of Asthma Exacerbations

Asthma exacerbations were recorded prospectively over a 12-month follow-up period. Exacerbations were defined as events requiring systemic corticosteroid therapy and/or resulting in emergency department visits, unscheduled outpatient visits, or hospitalizations related to asthma.

Statistical Analysis

The sample size was calculated based on an expected SAD prevalence of 70%, a 95% confidence level, and an absolute precision of approximately 10.5%, resulting in a minimum required sample size of 73 patients.² Continuous variables were expressed as mean ± standard deviation or median (interquartile range), while categorical variables were presented as counts and percentages. Between-group comparisons were performed using the independent samples t-test or Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables.

For comparisons involving more than two groups, one-way analysis of variance was used for normally distributed continuous variables, whereas the Kruskal-Wallis test was used for non-normally distributed variables. Associations between continuous variables were assessed using Spearman's rank correlation coefficient. To determine independent associations with clinical outcomes, multivariable regression models were constructed. Multiple linear regression, with HC3 heteroskedasticity-consistent robust standard errors, was used for the AQLQ total score, and ordinal logistic regression was used for the ACT control categories. Models were adjusted for age, sex, body mass index (BMI), and smoking exposure (pack-years). Further sensitivity analyses were conducted by separately adding spirometric indices ($FEV_1\%$ and $FEF_{25-75}\%$) to these models.

To assess potential selection bias due to missing questionnaire data, baseline characteristics of participants included in multivariable analyses ($n = 74$) were compared with those of participants not included ($n = 31$) (Supplementary Table S1). All analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA); a P value < 0.05 was considered statistically significant.

RESULTS

Study Population

The cohort consisted of 105 patients with asthma, of whom 78 (74.3%) were female. The mean age was 49.04 ± 13.00 years. Smoking status was available for 104 participants, of whom 73 (70.2%) were never-smokers, 17 (16.3%) were active smokers, and 14 (13.5%) were ex-smokers. The mean BMI was 27.76 ± 5.02 kg/m². Baseline demographic and clinical characteristics are summarized in Table 1.

Prevalence of Small Airway Dysfunction

SAD was identified by IOS in 63 (64.3%) patients with asthma. SAD status differed significantly across the five individual GINA

treatment steps ($P < 0.001$; Table 1). In a separate analysis that grouped patients into GINA steps 1–3 and 4–5, SAD was more frequent in the higher treatment-step group ($P < 0.001$).

Asthma Control and Small Airway Dysfunction

Mean ACT scores were significantly lower among patients with SAD than among those without dysfunction ($P = 0.021$). When patients were categorized according to ACT-defined asthma control levels (uncontrolled, partially controlled, and well-controlled), symptom control status was significantly associated with the presence of SAD ($P = 0.041$). Notably, SAD was present in 25 (92%) of the 27 patients with uncontrolled asthma. As shown in Table 2, asthma control assessed by the ACT was significantly associated with both oscillometry- and spirometry-derived indices of small airway function. Among IOS parameters, R5–R20 showed a moderate negative correlation

with ACT scores ($r = -0.366$), indicating poorer asthma control with increasing peripheral airway resistance. In contrast, the spirometric small airway index FEF_{25-75} demonstrated a weaker positive correlation with ACT scores ($r = 0.291$). These findings suggest that both methods reflect small airway involvement, but oscillometry-derived parameters are more strongly associated with symptom control.

Quality of Life Assessment

Health-related quality of life, assessed using the AQLQ, was significantly impaired in patients with SAD. Patients with SAD had lower mean AQLQ total scores than those without SAD (4.34 ± 1.27 vs. 5.43 ± 1.14 , $P = 0.002$) (Figure 1). As detailed in Table 3, patients with SAD also demonstrated significantly lower scores across multiple AQLQ subdomains, including symptoms, activity limitation, and emotional function,

Table 1. Baseline demographic, clinical, and pulmonary function characteristics of asthma patients

Demographic data	SAD present (R5–R20 ≥ 0.07) n = 63	SAD absent (R5–R20 < 0.07) n = 35	P value
Age, years, mean $\pm$ SD	53.90 $\pm$ 10.05	41.74 $\pm$ 13.60	<0.001
Sex, n (%), female	51 (81%)	21 (60%)	0.044
BMI, kg/m ² , mean $\pm$ SD	28.90 $\pm$ 5.11	26.02 $\pm$ 4.41	0.005
Smoking exposure, pack-years, mean $\pm$ SD	20.40 $\pm$ 10.89 (n = 12)	13.44 $\pm$ 8.40 (n = 10)	0.194
Cardiovascular comorbidities, n (%)	20/62 (32.3%)	8/35 (22.9%)	0.454
GINA treatment step, n (%)			
1	1/7 (14.3%)	6/7 (85.7%)	<0.001
2	4/14 (28.6%)	10/14 (71.4%)	
3	12/24 (50.0%)	12/24 (50.0%)	
4	20/26 (76.9%)	6/26 (23.1%)	
5	26/27 (96.3%)	1/27 (3.7%)	
FeNO, ppb, median (IQR)	18.00 (9.50–31.50) (n = 43)	19.50 (11.25–40.75) (n = 26)	0.264
Blood eosinophil count, $10^3/\mu\text{L}$ median (IQR)	0.37 (0.15–0.58)	0.30 (0.15–0.59)	0.648
Spirometry			
FVC % predicted	92.63 $\pm$ 19.16 (n = 62)	102.50 $\pm$ 17.24 (n = 31)	0.008
FEV ₁ % predicted	77.40 $\pm$ 21.09 (n = 62)	93.74 $\pm$ 16.36 (n = 31)	<0.001
FEV ₁ /FVC (%), median (IQR)	72.57 (64.00–77.91) (n = 62)	77.52 (72.59–79.52) (n = 31)	0.004
FEF ₂₅₋₇₅ % predicted, median (IQR)	44.00 (22.25–63.75) (n = 62)	66.00 (47.50–76.00) (n = 30)	0.002
Impulse oscillometry			
R5, mean $\pm$ SD	0.81 $\pm$ 0.33 (n = 63)	0.43 $\pm$ 0.12 (n = 32)	<0.001
R20, mean $\pm$ SD	0.46 $\pm$ 0.11 (n = 63)	0.38 $\pm$ 0.12 (n = 32)	0.002
AX, mean $\pm$ SD	4.98 $\pm$ 4.33 (n = 56)	1.16 $\pm$ 1.69 (n = 32)	<0.001
R5–R20, mean $\pm$ SD	0.34 $\pm$ 0.25 (n = 63)	0.05 $\pm$ 0.02 (n = 35)	<0.001
Fres, mean $\pm$ SD	30.92 $\pm$ 11.88 (n = 58)	19.63 $\pm$ 7.86 (n = 32)	<0.001
X5, mean $\pm$ SD	–0.46 $\pm$ 0.51 (n = 60)	–0.12 $\pm$ 0.15 (n = 32)	<0.001

Continuous variables are presented as mean $\pm$ standard deviation or median (interquartile range), according to data distribution. Categorical variables are presented as n (%). Numerical values are reported using decimal points. For variables with missing data, the number of available observations (n) is indicated. SAD classification based on R5–R20 ≥ 0.07 kPa-s-L⁻¹ was available for 98 of 105 participants (SAD present, n = 63; SAD absent, n = 35). Variable-specific denominators are reported where data were unavailable. Percentages were calculated using the number of participants with available data for each variable. Between-group P values are based on participants with available SAD classification and available data for the respective variable. Normally distributed continuous variables were compared using the independent-samples t-test, whereas non-normally distributed variables, including FEV₁/FVC and FEF₂₅₋₇₅, were compared using the Mann-Whitney U test. IOS parameters are reported according to device output units: R5, R20, R5–R20, and X5 in kPa-s-L⁻¹; Fres in Hz; and AX in kPa/L.

SAD: small airway dysfunction, BMI: body mass index, FeNO: fractional exhaled nitric oxide, FVC: forced vital capacity, FEV₁: forced expiratory volume in the first second, FEF₂₅₋₇₅: forced expiratory flow between 25% and 75%, AX: reactance area, R5–R20: difference between resistances at 5 and 20 Hz, Fres: resonant frequency in Hz, X5: reactance at 5 Hz, SD: standard deviation, IQR: interquartile range, GINA: Global Initiative for Asthma, IOS: impulse oscillometry

indicating an association between SAD and poorer patient-reported quality of life.

Exacerbation and Small Airway Dysfunction

During the 12-month prospective follow-up, exacerbations requiring systemic corticosteroids, emergency department visits, unscheduled outpatient visits, and asthma-related hospitalizations were recorded. Patients with IOS-defined SAD experienced more emergency department visits and a greater total exacerbation burden over 12 months than those without dysfunction ($P < 0.001$) (Table 3).

Inflammatory Biomarkers

FeNO levels and blood eosinophil counts were not significantly associated with IOS-defined SAD.

Independent Associations of SAD with Clinical Outcomes

Multivariable analyses were conducted to determine whether SAD was independently associated with asthma outcomes. R5–R20 was significantly associated with patient-reported outcomes after multivariable adjustment (Table 4). When modeled as a continuous variable, elevated R5–R20 values were independently associated with worse health-related quality of life. For each 0.1 kPa·s·L⁻¹ increase in R5–R20, the mean AQLQ score decreased by 0.18 points after adjustment for age, sex, BMI, and smoking history [$\beta = -0.18$; 95% confidence interval

(CI) -0.30 to -0.07 ; $P = 0.002$]. This association persisted in sensitivity analyses that additionally controlled for spirometric indices (FEV₁% and FEF₂₅₋₇₅%), whereas spirometric parameters themselves did not show statistically significant independent associations with AQLQ.

For asthma control, higher R5–R20 values were associated with poorer ACT-defined control categories in the adjusted ordinal logistic regression model (Table 4). Each 0.1 kPa·s·L⁻¹ increase in R5–R20 increased the odds of being in a worse control category by 33% [odds ratio (OR) 1.33; 95% CI 1.07 to 1.66; $P = 0.010$]. This association remained directionally consistent in models additionally adjusted for spirometric parameters, and reached borderline significance when FEF₂₅₋₇₅% was included (OR 1.26; 95% CI 1.00 to 1.58; $P = 0.049$), whereas it was attenuated after adjustment for FEV₁% predicted (OR 1.25; 95% CI 0.99 to 1.58; $P = 0.057$).

DISCUSSION

In the present study, SAD assessed by IOS was highly prevalent among adult patients with asthma and was significantly associated with poorer asthma control and reduced health-related quality of life. The association between R5–R20 and quality of life remained significant after additional adjustment for conventional spirometric indices, whereas the association with asthma control was attenuated after spirometric adjustment. These findings suggest that assessment of distal airway function

Table 2. Correlation between asthma control test scores and spirometric and impulse oscillometric parameters

Impulse oscillometric parameters		Asthma control test	Spirometric parameters		Asthma control test
R5	r	−0.373	FEV ₁	r	0.178
	P	0.001		P	0.129
	n	74		n	74
R20	r	−0.237	FVC	r	0.135
	P	0.042		P	0.251
	n	74		n	74
R5–R20	r	−0.366	FEV ₁ /FVC	r	0.239
	P	0.001		P	0.040
	n	74		n	74
X5	r	0.236	FEF ₂₅₋₇₅ %	r	0.291
	P	0.043		P	0.012
	n	74		n	74
Fres	r	−0.138	FEF ₅₀ %	r	0.286
	P	0.249		P	0.014
	n	72		n	74
AX	r	−0.200			
	P	0.095			
	n	71			

Correlation analyses were performed using available paired data. ACT data were available for 74 patients; Fres values were missing in 2 patients and AX values in 3 patients, resulting in n = 72 for Fres and n = 71 for AX. IOS parameters are reported according to device output units: R5, R20, R5–R20, and X5 in kPa·s·L⁻¹; Fres in Hz; and AX in kPa/L.

FVC: forced vital capacity, FEV₁: forced expiratory volume in the first second, FEF₂₅₋₇₅: forced expiratory flow between 25% and 75%, AX: reactance area, R5–R20: difference between resistance at 5 Hz and 20 Hz, Fres: resonant frequency in Hz, X5: reactance at 5 Hz, ACT: asthma control test, IOS: impulse oscillometry, FEF₅₀: forced expiratory flow at 50% of forced vital capacity

may provide complementary clinical information not fully captured by conventional spirometry.

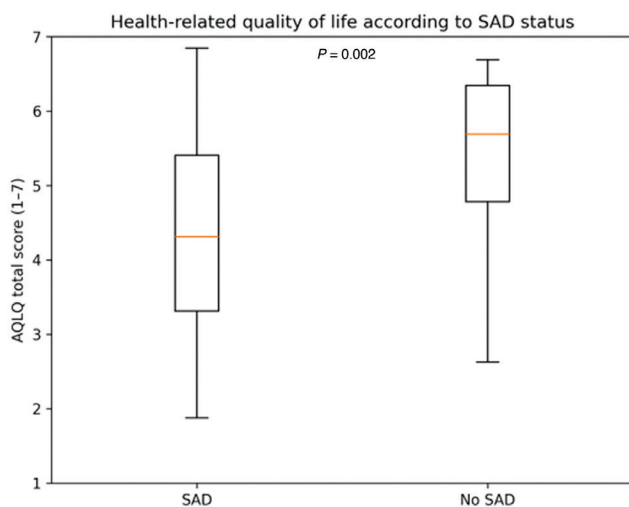


Figure 1. Health-related quality of life according to small airway dysfunction status. Boxplot showing total asthma quality of life questionnaire (AQLQ) scores in patients with and without small airway dysfunction defined by impulse oscillometry ($R5-R20 \geq 0.07$ kPa·s·L⁻¹). Patients with small airway dysfunction had significantly lower AQLQ total scores compared with those without dysfunction ($P = 0.002$)

SAD: small airway dysfunction

The high prevalence of SAD (64.3%) observed in our cohort is consistent with recent large-scale and real-world studies demonstrating that small airway abnormalities are pervasive across the asthma severity spectrum. Notably, the ATLANTIS study established that SAD represents a distinct and measurable trait, frequently present even in patients with preserved FEV₁ and minimal airflow limitation on spirometry.² This aligns with histopathological and physiological evidence suggesting that inflammation and remodeling of the distal airways contribute to ventilation heterogeneity and air trapping, often occurring independently of large airway obstruction.^{5,6}

Our results show that SAD is significantly associated with clinical status, with patients exhibiting an increased likelihood of poor asthma control. This finding aligns with growing evidence that oscillometry-derived parameters correlate more closely with symptom burden than conventional spirometry.^{9,23} Crucially, we observed that FEV₁ was preserved in many patients despite significant distal airway impairment, whereas FEF₂₅₋₇₅ showed substantial overlap between groups. These discrepancies highlight the “silent zone” in the lungs, where inflammation may persist undetected by routine flow-volume loops. The observation that elevated R5–R20 values were associated with worse asthma control in the primary adjusted model (although this association was attenuated after additional adjustment for spirometric indices) and with greater exacerbation burden suggests that SAD may reflect greater disease burden. Although SAD has been proposed as a potential treatable trait, our observational findings do not establish whether specifically targeting the distal airways improves clinical outcomes, and this

Table 3. Exacerbation rates, asthma control test and asthma quality of life questionnaire scores according to small airway dysfunction status

	According to IOS-defined small airway dysfunction status		P value
	SAD n = 57	No SAD n = 17	
Number of hospitalizations in 1 year* Median [IQR]	0 [0–0]	0 [0–0]	0.079
Number of emergency department visits in 1 year* Median [IQR]	1 [0–3]	0 [0–0]	<0.001
Total number of exacerbations in 1 year* Median [IQR]	3 [2–5]	2 [0–2]	<0.001
Asthma control test score**, mean ± SD	16.79±5.36	20.12±4.84	0.021
AQLQ symptoms**, mean ± SD	4.64±1.37	5.51±1.18	0.019
AQLQ activity limitation**, mean ± SD	4.44±1.29	5.51±1.21	0.006
AQLQ emotional function**, mean ± SD	3.97±1.68	5.82±1.40	<0.001
AQLQ environmental stimuli**, mean ± SD	3.58±1.70	4.44±1.80	0.069
AQLQ total score**, mean ± SD	4.34±1.27	5.43±1.14	0.002

Analyses in this table were restricted to patients with complete ACT, AQLQ, and 12-month follow-up data (n = 74). SAD was defined as $R5-R20 \geq 0.07$ kPa·s·L⁻¹

*Mann-Whitney U test, **Independent-samples t-test

IOS: impulse oscillometry, SAD: small airway dysfunction, ACT: asthma control test, AQLQ: asthma quality of life questionnaire, IQR: interquartile range, SD: standard deviation

Table 4. Independent association of IOS-derived small airway dysfunction (R5–R20) with asthma control and health-related quality of life		
Model	R5–R20 effect	Added spirometry term
Panel A. outcome: AQLQ total (OLS)		
Primary	–0.18 (–0.30 to –0.07); <i>P</i> = 0.002	–
+ FEV ₁ % predicted	–0.18 (–0.31 to –0.06); <i>P</i> = 0.004	–0.000 (–0.017 to 0.017); <i>P</i> = 0.987
+ FEF _{25–75} % predicted	–0.16 (–0.29 to –0.04); <i>P</i> = 0.010	0.006 (–0.012 to 0.024); <i>P</i> = 0.491
Panel B. outcome: ACT control category (ordinal logit)		
Primary	1.33 (1.07 to 1.66); <i>P</i> = 0.010	–
+ FEV ₁ % predicted	1.25 (0.99 to 1.58); <i>P</i> = 0.057	0.98 (0.96 to 1.01); <i>P</i> = 0.141
+ FEF _{25–75} % predicted	1.26 (1.00 to 1.58); <i>P</i> = 0.049	0.98 (0.95 to 1.00); <i>P</i> = 0.096
R5–R20 was modeled as a continuous predictor, scaled per 0.1 kPa·s·L ^{–1} increase. Models adjusted for age, sex, BMI, and smoking exposure (pack-years). Spirometric indices were added separately (sensitivity analyses). Panel A reports β coefficients with 95% confidence intervals and <i>P</i> values (HC3 robust standard errors). The β coefficient represents the change in the mean AQLQ total score associated with a 0.1 kPa·s·L ^{–1} increase in R5–R20. Panel B reports odds ratios (ORs) for being in a worse ACT control category with 95% confidence intervals and <i>P</i> values (ordinal logistic regression, logit link). Higher OR indicates poorer control. Note: FEV ₁ % and FEF _{25–75} % were entered in separate sensitivity models to avoid collinearity when both spirometric indices are included simultaneously. The AQLQ total score was calculated as the mean of the 32 item scores and ranges from 1 to 7, with higher scores indicating better asthma-related quality of life. Sample size: <i>n</i> = 74 for Panel A; <i>n</i> = 74 for Panel B		
ACT: asthma control test, AQLQ: asthma quality of life questionnaire, BMI: body mass index, IOS: impulse oscillometry, OLS: ordinary least squares, FEV ₁ : forced expiratory volume in the first second, FEF _{25–75} : forced expiratory flow between 25% and 75%, HC3: heteroskedasticity-consistent standard error estimator type 3		

question requires confirmation in prospective interventional studies.

Health-related quality of life was also significantly impaired in patients with SAD. Previous studies have reported weak or inconsistent associations between spirometric parameters and quality of life in asthma.²⁴ In contrast, recent investigations using IOS have demonstrated meaningful relationships between distal airway mechanics and patient-reported outcomes.^{12,14} Our findings suggest that SAD may contribute to limitations in daily activities, affect symptom perception, and impair emotional well-being—domains that are not adequately captured by conventional lung function tests and may therefore explain the observed dissociation between spirometric measurements and quality of life. Higher R5–R20 values were independently associated with lower health-related quality of life. Specifically, each 0.1 kPa·s·L^{–1} increase in R5–R20 was associated with an estimated 0.18-point decrease in the conventional 1–7 AQLQ score. Although this association was statistically significant, its magnitude was below the established minimal clinically important difference of 0.5 points and should therefore be interpreted cautiously in terms of clinical relevance.²⁵ The association remained significant after additional adjustment for FEV₁% predicted and FEF_{25–75}% predicted, suggesting that IOS-derived SAD may capture aspects of asthma-related burden not fully reflected by conventional spirometric indices.

In this study, we defined SAD based on a fixed cut-off value for R5–R20 (≥0.07 kPa·s·L^{–1}), rather than relying on percent predicted values.^{2,4,18} This fixed R5–R20 threshold was selected based on its use in the ATLANTIS study as an IOS measure of SAD in asthma.² While percent-predicted values are theoretically ideal, they are often limited by the variability of available reference equations across different populations. In contrast, a fixed cut-off offers a pragmatic advantage in routine clinical settings: it provides a standardized, easily applicable metric that does not require complex software calculations that depend on specific reference sets. The observed association between this threshold and patient-reported outcomes supports

its potential clinical utility, although further validation in larger cohorts is warranted.

In our cohort, patients with IOS-defined SAD were older, were more often female, and had a higher BMI. Because these findings were derived from unadjusted group comparisons, they should be interpreted cautiously. Nevertheless, they may indicate that demographic and anthropometric factors influence peripheral airway mechanics and the clinical expression of SAD. These observations are consistent with the concept that SAD represents a heterogeneous and clinically relevant trait in asthma.^{2,17} Further studies are needed to determine whether these factors independently contribute to IOS-defined SAD.

Study Limitations

Several limitations of this study should be acknowledged. Although exacerbation outcomes were assessed prospectively during a 12-month follow-up period, the baseline analysis was cross-sectional; therefore, causal inference between SAD and clinical outcomes remains limited. In addition, ACT and AQLQ data were available only for a subset of the study cohort. SAD was more frequent among participants included in the questionnaire-based analyses than among those not included. Furthermore, R5–R20 classification was unavailable in seven participants, all of whom belonged to the latter group. These differences indicate some degree of selection affecting the availability of complete data and may have influenced the observed prevalence of SAD. Accordingly, the prevalence estimate should be interpreted in the context of the available R5–R20 data and should be confirmed in larger cohorts with more complete IOS measurements. This selection may also have influenced the observed associations between SAD and patient-reported outcomes, and may limit the generalizability of these analyses. Detailed information on maintenance treatment for asthma and treatment adherence was not systematically available; therefore, treatment heterogeneity and non-adherence may have contributed to residual confounding. Because poor adherence to maintenance therapy may influence asthma control, exacerbation risk, quality of

life, and IOS-derived airway mechanics, future studies should incorporate standardized adherence assessment to better clarify the independent relationship between IOS-defined SAD and clinical outcomes. Although R5–R20 was selected as the primary IOS index for defining SAD, other IOS parameters, including X5 and AX, were evaluated and may provide complementary information on peripheral airway reactance and elastic properties. Future studies using composite IOS-based definitions may further improve the characterization of SAD in asthma. Nevertheless, the use of validated patient-reported outcome measures and standardized IOS assessment based on contemporary guidelines strengthens the validity of our findings.

CONCLUSION

This study demonstrates that SAD is a frequent feature of asthma. Higher R5–R20 was independently associated with poorer quality of life; this association remained significant after additional adjustment for conventional spirometric indices. Higher R5–R20 was also associated with poorer asthma control in the primary adjusted model, although this association was attenuated after additional spirometric adjustment. Additionally, IOS-defined SAD was associated with a greater exacerbation burden during follow-up. These findings suggest that IOS may provide complementary information on small airway involvement.

Ethics

Ethics Committee Approval: The study protocol was approved by the Mersin University Clinical Research Ethics Committee (decision no: 2019/199, dated: 08.05.2019) and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Informed Consent: Individuals who met the inclusion criteria, did not meet any exclusion criteria, and provided written informed consent were enrolled.

Footnotes

Authorship Contributions

Surgical and Medical Practices: D.P.Y., S.N., E.S.Ö., C.Ö., Concept: D.P.Y., S.N., E.S.Ö., C.Ö., Design: D.P.Y., S.N., B.T., E.S.Ö., C.Ö., Data Collection or Processing: D.P.Y., S.N., B.T., Analysis or Interpretation: D.P.Y., S.N., B.T., Literature Search: D.P.Y., S.N., B.T., Writing: D.P.Y., S.N., B.T., E.S.Ö., C.Ö.

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