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ORIGINAL RESEARCH

Small Airways Disease Adversely Impacts the Response to Biologic Therapies in Severe Asthma

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ABSTRACT

***Introduction*:** Small airways disease (SAD) is increasingly recognized as a relevant trait in severe asthma, but its influence on outcomes with biologic therapies remains uncertain. We assessed the prevalence of SAD and its association with real-world treatment response in a severe asthma cohort. We hypothesized that baseline SAD, particularly when identified by oscillometry, would be associated with non-response to biologic therapy over 12 months.

***Methods*:** This single-center, retrospective cohort included adult severe asthma outpatients initiating biologic therapy. At enrolment, participants underwent clinical and biomarker evaluation, complete lung function testing (spirometry/plethysmography), and the Forced Oscillation Technique. SAD was defined by the coexistence of ≥ 1 oscillometry abnormality and ≥ 1 spirometry/plethysmography abnormality. "Non-responders" were defined as patients experiencing ≥ 2 exacerbations during 12-month follow-up. Multivariable logistic regression was used to identify independent predictors of response, adjusting for biologic therapy and key confounders (including BMI).

***Results*:** The analytic sample comprised 156 patients (aged 55 ± 18 years, 91 females) treated with omalizumab ($n = 60$), benralizumab ($n = 23$), mepolizumab ($n = 32$), or dupilumab ($n = 41$). After 12 months, 24/156 patients (15%) were classified as non-responders. At baseline, SAD was present in 69/156 patients (44%) and was more prevalent in non-responders than in responders (75% vs. 40%, $p < 0.01$). Non-responders showed worse spirometric indices (FEV_1% and FEV_1/VC) and more abnormal oscillometry (lower X5exp and higher ΔXrs, R5exp, and R5-R19). In multivariable models adjusted for biologic and key confounders, baseline oscillometry abnormalities were independently

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associated with a reduced odds of response (adjusted OR 0.08, 95% CI 0.02–0.37; $p=0.001$). ***Conclusions***: In a real-world severe asthma cohort, baseline SAD, particularly when identified by oscillometry, was associated with subsequent non-response to biologic therapy, suggesting potential value for risk stratification.

Keywords: Asthma endotypes; Biologic therapies; Forced oscillation technique; Severe asthma; Small airways

Key Summary Points

Why carry out this study?

Small airways disease (SAD) is common in severe asthma, but its impact on real-world response to biologic therapies remains uncertain.

Identifying pragmatic physiological markers associated with poor response could support risk stratification and personalized follow-up in routine care.

What did the study ask?

We asked whether baseline SAD, defined using oscillometry combined with spirometry/plethysmography, was associated with non-response to biologic therapy over 12 months.

What was learned from the study?

In 156 biologic-treated severe asthma outpatients, 15% were non-responders at 12 months, and baseline SAD was more frequent in non-responders than responders (75 vs. 40%).

Oscillometry-defined SAD was independently associated with a lower probability of response in multivariable models, suggesting that baseline oscillometry may help identify patients at higher risk of suboptimal outcomes.

INTRODUCTION

Severe asthma (SA) is defined as asthma that remains uncontrolled despite adherence to optimized high-dose inhaled corticosteroid (ICS) and long-acting beta-agonist (LABA) therapy, correct inhaler technique, and appropriate management of comorbidities and environmental exposures, or that worsens when ICS-LABA treatment is reduced [1]. Although SA affects only approximately 5–10% of the overall asthma population, it accounts for a disproportionate share of asthma-related healthcare utilization and costs compared to mild-to-moderate disease asthma [1].

Over the past two decades, biologic therapies have substantially improved outcomes in SA, including reduction in exacerbation rates, systemic corticosteroid exposure and related adverse events, and missed school or working days [2]. However, a subset of patients treated with biologics do not achieve these goals despite appropriate phenotyping and fulfillment of treatment eligibility criteria [3]. Moreover, there is no current universally accepted definition of remission or non-response to therapy in SA, contributing to heterogeneity across studies and clinical uncertainty in routine care [3, 4].

In patients who do not respond to biologic therapies (commonly referred to as "non-responders"), management becomes particularly challenging because therapeutic options are limited and the burden of symptoms, exacerbations, and impaired quality of life often persists. The mechanisms underpinning non-response are incompletely understood and may include genetic variability, immune dysregulation, unrecognized inflammatory pathways or pharmacokinetic differences in drug metabolism [3, 4]. Another plausible contributor is involvement of the small airways, defined as non-cartilaginous airways ≤2 mm in internal diameter (approximately 8th to 23rd airway generations) [5]. In small airways disease (SAD), the inflammation, remodeling, and smooth-muscle hypertrophy lead to luminal narrowing and dysfunction that may contribute to air trapping, hyperinflation, and exertional dyspnea [5].

Because no single gold-standard diagnostic test exists for SAD in routine practice, distal airway dysfunction is typically inferred using physiological surrogates. These included reduced mid-expiratory flows (e.g., $FEF_{25–75}$ < 65% predicted) [6], increased static hyperinflation indices (e.g., RV> 120% 120% predicted) [7, 8], and an abnormal small-airway closure measure on multi-breath nitrogen washout (e.g., closing volume) [9]. More recently, the Forced Oscillation Technique (FOT) has re-emerged as a practical tool and effort-independent method for peripheral airway mechanics by measuring respiratory system resistance (Rrs) and reactance (Xrs) at different frequencies, with growing evidence supporting its utility in characterizing SAD in SA [10]. Given the links between SAD, disease severity, and clinical outcomes, it is plausible that SAD contributes to suboptimal response to biologic therapy; however, its prognostic value in real-world cohorts remains insufficiently defined.

Therefore, this study aimed to i) estimate the prevalence and characteristics of SA patients unresponsive to biologic therapy, ii) estimate the prevalence of baseline SAD in a real-world SA cohort, and iii) identify baseline physiological parameters independently associated with non-response over follow-up. We hypothesized that SAD, particularly when identified by combined oscillometric and spirometric abnormalities, is associated with a higher likelihood of non-response to biologic therapies, consistent with a functionally distinct SA trait/endotype.

METHODS

This is a single-center, retrospective cohort study. Adult patients referred to the Severe Asthma Clinic at the Careggi University Hospital (Florence, Italy), from January 2020 to December, 2023 were studied. The study used data from the SANI Registry (Severe Asthma Network in Italy), a national registry established in accordance with the Agency for Health Care Research and Quality *Registries for Evaluating Patient Outcomes* (3rd edition) The SANI Registry protocol received ethics approval from the appropriate Ethics Committees (coordinating center and participating sites). All participants provided written informed consent for inclusion in the SANI Registry and for the use of their de-identified data for research purposes. Inclusion criteria were: i) a diagnosis of SA according to GINA criteria [1]; ii) eligibility for biologic therapies at enrolment (T0); and iii) continuation of biologic treatment at 12 months (T1). As this was an observational cohort study, patients were classified as responders or non-responders (see below) after 12-month follow-up according to the prespecified outcome definition; groups were, therefore, not matched at baseline.

Outcome Definitions (response/non-response)

Asthma exacerbations were defined as worsening of the disease requiring systemic corticosteroids for ≥ 3 days and/or an emergency department visit or hospitalization for asthma requiring systemic corticosteroids [11]. Courses of systemic corticosteroids prescribed for asthma (including those issued in primary care) were counted as exacerbations irrespective of the healthcare setting, whereas those prescribed for non-asthma indications were excluded. Events involving both an acute care visit and systemic corticosteroids were counted once. A patient who experienced ≥ 2 severe exacerbations during the 12-month follow-up was a priori classified as non-response to biologic therapy; otherwise, the patient was classified as a responder.

Baseline Assessment

At baseline (T0), we collected demographics, clinical characteristics (including comorbidities), Asthma Control Test (ACT) score [12], laboratory data (blood eosinophil count, total serum IgE), fractional exhaled nitric oxide (FeNO), lung function, and forced oscillation technique parameters. FENO (FENO+, Medisoft Sorinnes, Belgium) was measured at 50 and 150 ml/s. Spirometry and plethysmographic lung volumes (V6200 Autobox Body

Plethysmograph Sensor Medics, Yorba Linda, CA) were assessed according to the ATS/ERS guideline [13]. Oscillometry (Resmon ProFULL, Restech Srl, Milan, Italy) was performed according to the European technical standards [14]. Respiratory system resistance (Rrs) and reactance (Xrs) were obtained during tidal breathing at 5- and 19-Hz frequencies; inspiratory and expiratory values were recorded. R5-R19 and ΔXrs (difference between Xinsp—Xexp) were calculated and X5exp was used as an indicator of distal airways involvement.

Definition of Small Airway Disease

Small airway disease was defined using the following criteria:

A) *Oscillometry abnormality* in line with current technical standard [14], oscillometry results were interpreted using available reference equations and limits of normal (LLN/ULN), recognising that thresholds may vary by device, population, and reference set. Because oscillometry cut-offs for small-airways dysfunction differ across studies and populations [15], we applied both i) an LLN-based reactance criterion and ii) a pragmatic index of frequency dependence of resistance. Specifically, oscillometry abnormality as X5exp < LLN and/or R5–R19 > 0.03 $kPa \cdot s \cdot l^{-1}$. The Resmon Pro reports resistance at 19 Hz (rather than 20 Hz); thus, R5–R19 represents the closest analogue to the commonly reported R5–R20 index. The 0.03 $kPa \cdot s \cdot l^{-1}$ cut-off has been widely used in asthma studies and was cited within the ATLANTIS program [16] as an established abnormality cut-off for R5–R20. We included expiratory reactance because within-breath indices may capture phase-specific distal airway abnormalities that can be attenuated when averaged over the whole breath.
B) *Spirometry/plethysmography abnormality* RV > 120% predicted or FEF_{25-75} < 65% predicted.
C) *Composite SAD* concurrent presence of both oscillometry and spirometry/plethysmography abnormalities.

Data Analysis

Continuous variables were expressed as mean ± 95% confidence interval (CI) and categorical variables as *n* (%). Comparisons between responders and non-responders were performed using Student's *t* test for independent samples (continuous variables) and Fisher's exact test (categorical variables). To evaluate whether physiological parameters suggestive of small-airway involvement were independently associated with non-response, we fitted multivariate logistic regression models with non-response at 12 months as the dependent variable. Three models were specified a priori, and each included biologic therapy and key clinical/inflammatory covariates (e.g., ACT and biomarker data). Model 1 included dichotomous indicators of oscillometry abnormality and spirometry/plethysmography abnormalities (as defined above). Model 2 included individual component variables (X5exp < LLN, R5-R19 >0.03 $kPa \cdot s \cdot l^{-1}$, RV% > 120%, FEF_{25-75}% < 65%). Model 3 included the composite SAD definition. In all instances, significance was set at $p < 0.05$. Data analyses were performed using SPSS 177 v30.0 (IBM, Armonk, NY, USA), GraphPad Prism (version 10.0.03)

RESULTS

We examined 160 adult outpatients (91 females, 57%) with a mean age of 55 ± 18 years (range 18–85 years). Four patients were excluded because they switched to a different biologic therapy during follow-up; therefore, 156 patients were included in the outcome analyses and treated with omalizumab (*n* = 60), benralizumab (*n* = 23), mepolizumab (*n* = 32), or dupilumab (*n* = 41). Baseline demographic, clinical, and laboratory data are reported in Table 1. After 12 months, 24/156 patients (15%) were non-responses. Overall, baseline, SAD was present in 69/156 (44%) patients and was more frequent among non-responders than responders (75 vs.

Table 1 Baseline demographic, clinical and laboratory data of the overall cohort and stratified by treatment response at 12 months (responders vs. non-responders)

	Whole population (*n* = 156)	**responders (*n* = 132)**	**non-responders (*n* = 24)**	***p* value**
Age, years	55 (18)	55 (18)	55 (17)	NS
Family history of asthma, *n* (%)	58 (37)	35 (26)	10 (42)	NS
Female sex, *n* (%)	91 (58)	74 (56)	17 (70)	
Male sex, *n* (%)	65 (42)	58 (44)	7 (30)	
Current smokers, *n* (%)	32 (20)	28 (21)	4 (17)	NS
Ex-smokers, *n* (%)	41 (26)	35 (26)	6 (25)	NS
Smoking history, packs/year	7 (12)	7 (13)	7 (9)	NS
Age at diagnosis, years	22 (15)	23 (15)	21 (11)	NS
Body mass index, kg/m^2	27.4 (6)	26.9 (5)	28.1 (6)	NS
ACT	15 (4)	15 (5)	14 (4)	NS
FEV_1 (% pred.)	72.78 (23.10)	75.05 (22.46)	59.88 (22.92)	
Medications:	36 (23)	30 (23)	6 (25)	
ICS/LABA	120 (77)	102 (77)	18 (75)	
ICS/LABA/LAMA	23 (15)	19 (14)	4 (16)	
OCS				
Blood eosinophils, × 10^9/l	0.58 (0.63)	0.60 (0.59)	0.52 (0.83)	NS
Blood neutrophils, × 10^9/l	4.16 (1.96)	4.07 (1.87)	4.62 (2.49)	NS
Total IgE, kU/l	633 (1333)	605 (1250)	654 (1655)	NS
FeNO 50 ml/s, ppb	32 (30)	33 (31)	27 (20)	NS
FeNO 150 ml/s, ppb	27 (27)	27 (30)	23 (17)	NS

Data are presented as mean (SD) unless otherwise indicated; categorical variables are shown as *n* (%). *p* values refer to comparisons between responders and non-responders (Student's *t* test or Fisher's exact test, as appropriate)

NS not significant, *ICS* inhaled corticosteroid, *LABA* long-acting beta-agonists, *LAMA* long-acting muscarinic antagonist, *OCS* maintenance oral corticosteroid

40%, $p < 0.01$). Regarding comorbidities (Fig. 1), gastroesophageal reflux disease (GERD) was slightly more prevalent among non-responders than responders (63% vs. 44%; p=0.05).

Spirometric indices, including FEV_1% predicted, $FEF_{25–75}$% predicted and FEV_1/VC were significantly ($p < 0.05$) lower in non-responders than responders (Fig. 2). Oscillometry showed a higher prevalence of abnormalities among non-responders. In more details, X5exp was lower ($p < 0.01$), whereas ΔXrs, R5exp, and R5-R19 were higher ($p < 0.05$) in non-responders than responders (Fig. 2). Specifically, R5-R19 > 0.03 kPa·s·l^{-1} was present in 79% of non-responders versus 38% of responders ($p < 0.01$), and X5exp < LLN in 67% vs. 21% ($p < 0.01$). In contrast, the prevalence of RV > 120% predicted and $FEF_{25–75}$< 65% predicted did not differ significantly between groups (Table 2). The proportion of non-response patients was similar across biologic agents (benralizumab

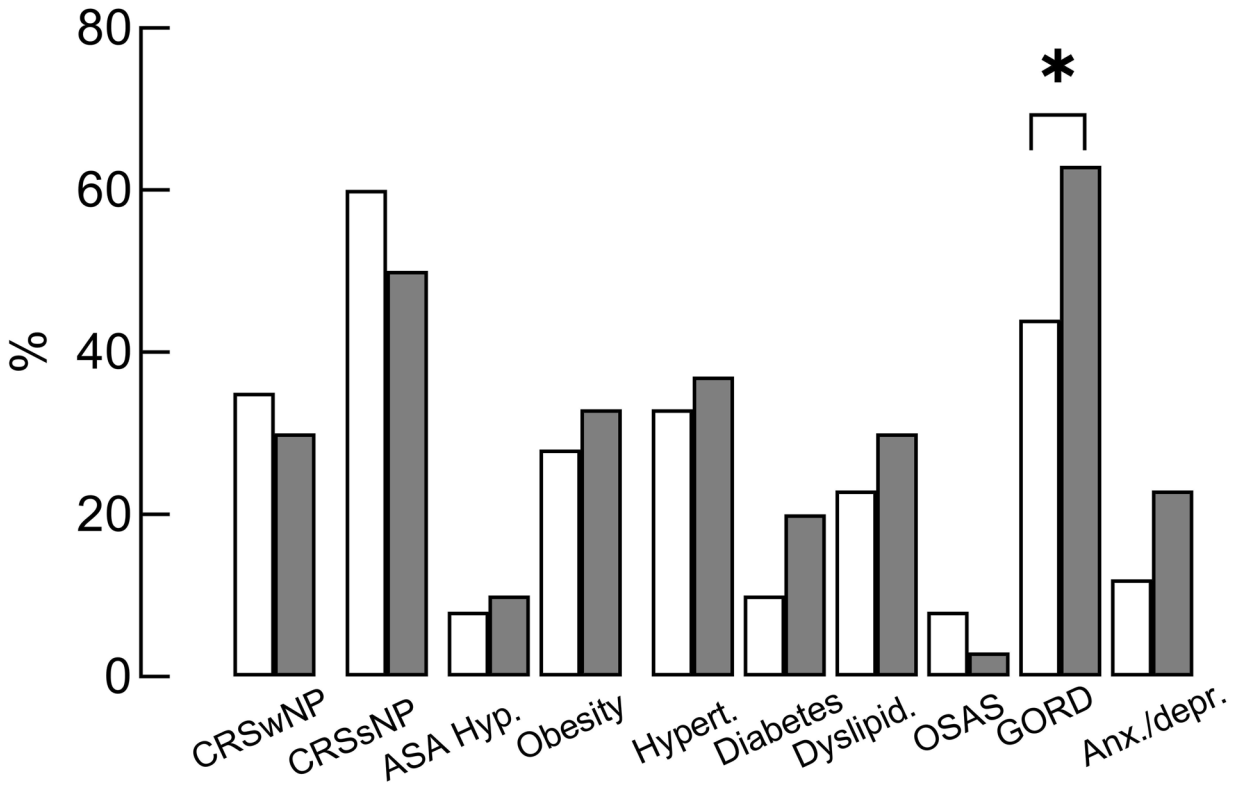

Fig. 1 Prevalence of comorbidities in responder (*white bars*) and non-responder (*grey bars*) patients. Data are shown as percentages (responders $n = 132$; non-responders $n = 24$). *$p < 0.05$ for between-group comparison (Fisher's exact test). *CRSwNP* chronic rhinosinusitis with nasal polyps, *CRSsNP* chronic rhinosinusitis without nasal polyps, *ASA Hyper.* acetylsalicylic acid hypersensitivity, *Anx/depr.* anxiety/depression, *Hypert.* hypertension, *Dyslipid.* dyslipidemia, *GORD* gastroesophageal reflux disease, *OSAS* obstructive sleep apnea syndrome

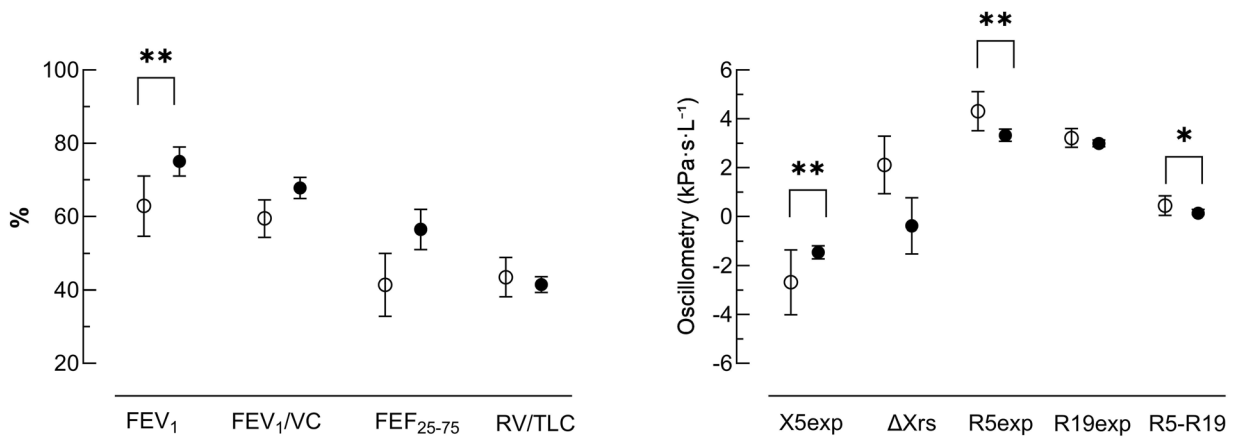

Fig. 2 Baseline spirometric/plethysmographic (*left panel*) and oscillometry (*right panel*) parameters in responders (*empty circles*) and non-responders (*filled circles*) to biologic therapy at 12 months. Data are shown as mean (95% CI). *, p value < 0.05, **, p value < 0.01 for between-group comparisons

Table 2 Proportion of responders and non-responders meeting criteria for small airway disease (SAD)

	Responders ($n = 132$)	Non-responders ($n = 24$)	*P* value
R5-R19 > 0.03 kPa·s·l^{-1}	38%	79%	< 0.01
X5exp < LLN	21%	67%	< 0.01
RV > 120% predicted	47%	67%	NS
$FEF_{25–75}$ < 65% predicted	77%	87%	NS
Composite SAD	40%	75%	< 0.01

Values are percentages; *p* values compare responders vs. non-responders (Fisher's exact test). Composite SAD was defined as the coexistence of ≥ 1 oscillometry abnormality and ≥ 1 spirometry/plethysmography abnormality

NS not significant; see Methods for further details

17.4%, dupilumab 14.6%, mepolizumab 15.6%, and omalizumab 23.3%).

After adjustment for biologic therapy and other covariates, measures of small-airways dysfunction remained independently associated with non-response (Table 3). In model 1 (Table 3), oscillometry abnormality was independently associated with a lower probability of response (OR 0.08, $p = 0.001$). In model 2, both R5-R19 > 0.03 kPa·s·l^{-1} (OR 0.11, $p = 0.008$) and X5exp < LLN (OR 0.08, $p = 0.001$) were independently associated with reduced odds of response. In model 3, the composite SAD definition (concurrent oscillometry and spirometric/plethysmography abnormalities) remained significantly associated with reduced odds of response after adjustment for biologic therapy and other covariates (OR 0.14, $p = 0.004$).

DISCUSSION

This study investigated the prevalence and clinical impact of SAD on treatment response in patients with SA receiving biologic therapies in routine care. Small airways disease, defined by the coexistence of oscillometric and spirometric/plethysmographic abnormalities, was more prevalent in patients who subsequently met criteria for non-response to biologic agents at 12 months. Furthermore, oscillometry indices, particularly R5–R19 and X5exp, were independently associated with non-response, whereas spirometric/plethysmographic surrogates and type 2 biomarkers (blood eosinophils, total IgE, and FeNO) were not.

In recent years, increasing attention has focused on distal airway involvement in asthma [17]. Small airways pathology is characterized by inflammatory cells infiltration, airway remodeling, smooth muscle hypertrophy and altered airway–parenchymal interdependence, which collectively contribute to airflow limitation, air trapping and symptoms such as exertional dyspnea and poor asthma control [17, 18]. In this context, SAD has emerged as a clinically relevant trait that may contribute to disease severity and variability in treatment outcomes.

Larger studies, such as the ATLANTIS, have characterized SAD using multiple pathophysiological tools, including mid-expiratory flows, oscillometry, and multibreath nitrogen washout, demonstrating progressive impairment of small airway indices with increasing disease severity [16]. In moderate-to-severe asthma, combined impairment of conventional spirometric and oscillometry indices has been associated with worse lung function, poorer quality of life, and a higher exacerbation burden, supporting an additive role for oscillometry in capturing distal airway dysfunction [5]. Alfieri et al. [19] also reported an association between oscillometry-defined small airway dysfunction and bronchial hyperresponsiveness in mild-to-moderate asthma, suggesting that SAD may contribute to persistent symptoms and variability in treatment response. In line with these observations, our findings suggest that baseline SAD may contribute to a delayed or attenuated response to biologic therapy in SA.

To date, studies evaluating treatment outcomes in SA patients with SAD treated with biologics have yielded heterogeneous results [20–28]; moreover, interpretation is complicated by the lack of a universally accepted definition of remission or non-response [4, 29–36]. Recent real-world prospective data have

Table 3 Multivariable logistic regression models evaluating baseline predictors of response to biologic therapy at 12 months

	Model 1			Model 2			Model 3		
Variables	**OR**	**CI**	***P* value**	**OR**	**CI**	***P* value**	**OR**	**CI**	***P* value**
Benralizumab	1			1			1		
Dupilumab	1.65	0.21–12.64	0.63	7.96	0.69–91.59	0.10	1.62	0.22–11.62	0.64
Mepolizumab	2.12	0.34–13.36	0.42	4.71	0.55–40.24	0.16	2.14	0.36–12.75	0.40
Omalizumab	1.27	0.24–6.86	0.77	3.02	0.46–19.86	0.25	1.30	0.26–6.44	0.75
Age	1.03	0.99–1.07	0.12	1.05	1.00–1.09	0.04	1.02	0.99–1.05	0.18
Sex (female 1, male 0)	1.06	0.34–3.28	0.92	1.20	0.35–4.12	0.77	0.89	0.30–2.59	0.83
BMI	1.00	0.90–1.12	0.98	1.00	0.87–1.14	0.99	1.00	0.90–1.11	0.96
Smoking habit	0.56	0.19–1.71	0.31	0.79	0.22–2.76	0.71	0.60	0.21–1.77	0.36
Oscillometry abnormality	0.08	0.02–0.37	0.001	–	–	–	–	–	–
Spirometry/plethysmography abnormality	0.66	0.11–4.14	0.66	–	–	–	–	–	–
R5-R19 > 0.03 kPa·s·L^{-1}	–	–	–	0.11	0.02–0.57	0.008	–	–	–
X5exp < LLN	-	–	–	0.08	0.02–0.37	0.001	–	–	–
RV > 120% predicted	–	–	–	0.59	0.17–2.01	0.39	–	–	–
FEF_{25-75} < 65% predicted	–	–	–	0.31	0.05–1.88	0.20	–	–	–
Composite SAD	–	–	–	–	–	–	0.14	0.04–0.53	0.004
ACT	1.01	0.89 – 1.13	0.93	1.04	0.91–1.19	0.52	1.01	0.90–1.14	0.81
FeNO 50 ml/s, ppb	1.01	0.98 – 1.05	0.50	1.02	0.98 1.06	0.38	1.01	0.98–1.04	0.49
FeNO 150 ml/s, ppb	0.99	0.96 – 1.03	0.67	0.99	0.96- 1.02	0.49	1.00	0.97–1.03	0.748
Eosinophils, × 10^9/l	1.21	0.41 – 3.57	0.73	1.00	0.28–3.59	0.99	1.22	0.43–3.48	0.71
Neutrophils, × 10^9/l	0.81	0.59 – 1.10	0.18	0.80	0.56–1.14	0.22	0.82	0.61–1.10	0.19
Total IgE, kU/l	1.00	1.00 – 1.00	0.45	1.00	1.00–1.00	0.37	1.00	1.00–1.00	0.54
Constant	11.53	0.12 – 1087	0.29	5.03	0.03–775	0.53	5.54	0.09–358	0.42

The dependent variable was response (responder = 1, non-responder = 0); odds ratios (OR) are shown with confidence intervals (CI) and *p* value. Model 1 includes composite indicators of oscillometry abnormalities and spirometry/plethysmography abnormalities; model 2 includes individual oscillometry/spirometry variables; model 3 includes the composite SAD definition. OR < 1 indicates lower odds of response

shown improvements in symptoms and non-oscillometric indices after biologic initiation, whereas oscillometry parameters may remain unchanged, underscoring the heterogeneity of small-airway responses across measurement technique [37]. Importantly, our findings should not be interpreted as an argument against the use of biologics in patients with SAD. Rather, they suggest that the presence of SAD may help identify a subgroup of SA patients at higher risk of suboptimal outcomes who may benefit from more individualized management such as closer monitoring, longer observation periods before judging response, and adjunctive strategies (e.g.,

optimization of inhaled delivery, airway clearance support, or targeted rehabilitation).

Although this study was not designed or powered to compare efficacy across individual biologic agents, we explored response proportions by treatment and observed broadly similar non-response rates across omalizumab, benralizumab, mepolizumab, and dupilumab. In multivariable models, we therefore adjusted for biologic therapy to account for potential class-related differences. Larger prospective studies with adequate sample size within each biologic class are needed to determine whether the prognostic value of oscillometry-defined SAD differs by mechanism of action.

Our study was designed to evaluate the prognostic value of baseline SAD rather than to quantify treatment-induced changes in small-airway mechanics. Published data on the effects of biologics on oscillometry/IOS-defined SAD remain limited and heterogeneous, often based on small cohorts, variable follow-up, and differing SAD definitions (fixed cut-offs vs. ULN/LLN; IOS vs. FOT; whole-breath vs. within-breath indices), Nevertheless, recent evidence suggests that biologics may improve small-airway indices over time in some patients, including reports with mepolizumab and dupilumab, and emerging real-world data with tezepelumab, with some evidence indicating progressive improvements, particularly with dupilumab [37–40]. Importantly, many studies focus on within-patient changes after biologic initiation rather than on whether baseline SAD predicts subsequent non-response. Differences in outcome definitions, follow-up duration, baseline inhaled regimen (including high use of extra-fine triple therapy), and the absence of longitudinal oscillometry in our dataset may therefore explain why baseline SAD appeared prognostic in our cohort. Prospective studies incorporating serial oscillometry are needed to determine whether changes in small-airway mechanics mediate clinical response and whether this varies by biologic mechanism of action.

Defining response to biologic treatments in SA remains controversial, with substantial variability across studies and no universally accepted definition. In this real-world cohort, we therefore adopted an event-based definition focused on clinically meaningful outcomes over 12 months, defining non-response as ≥ 2 severe exacerbations (requiring systemic corticosteroids and/or ED visit/hospitalization). We acknowledge that treatment response exists on a continuum, and that dichotomization may reduce information; therefore, our responder classification should be interpreted as a pragmatic approach to enable clinically interpretable subgroup comparisons rather than as a measure of diagnostic "specificity". Future studies should evaluate response using both event-based and as a continuum, possibly incorporating symptom scores, lung function trajectories, and biomarkers to improve comparability across studies and clinical applicability.

Traditionally, surrogate measurements of SAD in routine practice have included $FEF_{25–75}$ < 65% predicted and RV >120% predicted. While informative, these metrics may be insensitive or non-specific for peripheral airway involvement, particularly when interpreted in isolation [41]. Oscillometry provides an effort-independent assessment of respiratory mechanics by measuring resistance and reactance during tidal breathing, and its clinical role has been facilitated by European technical standardization [14]. In real-world practice, incorporating oscillometry may support risk stratification and more individualized follow-up (e.g., closer monitoring and adjunctive strategies) in patients with evidence of SAD. In the present study, we included within-breath oscillometry indices because whole-breath averages can mask phase-specific abnormalities: expiratory reactance, in particular, may capture distal airway closure and expiratory flow limitation that are less evident in full-breath measures. While ΔXrs has been used as a marker of expiratory flow limitation in COPD, its thresholds and interpretation may differ across diseases and devices; therefore, we used these indices primarily to characterize small-airway mechanics rather than to diagnose expiratory flow limitation per se. Furthermore, we used a commonly applied cut-off for R5–R19 to define distal airway dysfunction; although alternative thresholds have been proposed, we did not evaluate multiple cut-points in the present analysis, which may limit comparability across.

From a treatable-traits perspective, small airways dysfunction may be amenable to optimization of inhaled therapy, including the use of triple therapy and, where appropriate, extra-fine particle formulations that may improve peripheral deposition. In our cohort, a substantial proportion of patients were already receiving extra-fine ICS/LABA/LAMA triple therapy at baseline, which may have mitigated between-group differences in conventional spirometric surrogates; nevertheless, oscillometry-defined SAD remained associated with non-response, supporting its potential prognostic value beyond baseline inhaled regimen.

The retrospective, single-center design is an acknowledged limitation. Nevertheless, the real-world nature of the cohort enhances clinical relevance, as patients were treated under routine care conditions rather than within the constraints of highly selected randomized trial populations. Oscillometry (and the composite SAD classification) was assessed only at baseline; we did not perform post-treatment oscillometry measurements, and, therefore, we cannot determine whether biologic therapy modified small-airway function over time or whether changes in SAD mediated the observed clinical outcomes. Accordingly, we cannot determine whether non-responders had persistently worse SAD at 12 months than responders, or whether longitudinal changes in oscillometry tracked clinical response. In addition, the sample size within each biologic group was limited, precluding meaningful head-to-head comparisons between biologic agents. Despite these limitations, the study supports the hypothesis that baseline SAD may have prognostic value in biologic-treated severe asthma. Larger prospective, multicenter studies incorporating longitudinal oscillometry and complementary small-airway assessments are warranted to refine the risk stratification and asthma endotyping.

CONCLUSIONS

Small airway disease was common in this real-world severe asthma cohort and was associated with subsequent non-response to biologic therapy. While biologics remain essential for many patients with SA, baseline evidence of SAD, particularly by oscillometry, may help identify individuals at higher risk of suboptimal outcomes and support more individualized follow-up and adjunctive management. Prospective, multicenter studies are necessary to validate these findings and to determine how best to integrate small airway assessment into treatment algorithms and monitoring strategies.

Author Contributions. The authors meet the criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). Chiara Allegrini and Gianna Camiciottoli take responsibility for the integrity of the data and contributed substantially to the study design. Alessia Catalisano, Greta Insalata, Rubina Giulia Girolamo, Martina Maria Marinato, Luca Paita. Alessandra Sorano and Clara De Filippis enrolled patients and performed all study procedures. Chiara Marzi performed statistical analysis. Chiara Allegrini, Elisa Bentivegna, Federico Lavorini, and Gianna Camiciottoli were involved in the interpretation of the data, in drafting and critically revising the content of the manuscript. All authors had full access to all of the data in the study and approved the final version of the manuscript for publication.

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Data Availability. The authors confirm that all the data supporting the findings of this study are included in the article. Any additional materials related to this article can be obtained upon reasonable request from the corresponding authors.

Declarations

Conflict of interest. Elisa Bentivegna, Alessia Catalisano, Greta Insalata, Rubina Girolamo R. G., Martina Marinato M. M., Luca Paita, Marzi C, Alessandra Sorano, and Clara De Filippis C. declare no conflicts of interest. Federico Lavorini received research grants from GlaxoSmithKline

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Ethical Approval. This study used de-identified data from the SANI Registry (Severe Asthma Network in Italy). The SANI Registry protocol was approved by the relevant Ethics Committee(s) (coordinating center and participating sites, as applicable). All participants provided written informed consent for inclusion in the SANI Registry and for the use of their de-identified data for research purposes.

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