Original Article

Frequency and Clinical Relevance of Residual Bronchodilator Responsiveness in Adults With Asthma

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What is already known about this topic? Bronchodilator responsiveness (BDR) reflects airflow variability in asthma and is typically assessed after withholding therapy; the relevance of residual BDR under ongoing anti-inflammatory or bronchodilator treatment remains unclear.

What does this article add to our knowledge? Residual BDR is frequent in adults with asthma and correlates with refractory type 2 inflammation and features of inadequately controlled disease, including airflow obstruction, small airway dysfunction, frequent symptoms, and exacerbations.

How does this study impact current management guidelines? Residual BDR may serve as a simple, global marker to identify residual disease burden and guide treatment optimization in routine clinical care.

BACKGROUND: Bronchodilator responsiveness (BDR) reflects airflow variability in asthma and is typically assessed after withholding therapy. However, its relevance under ongoing maintenance therapy remains unclear.
OBJECTIVE: To investigate the frequency and clinical relevance of residual bronchodilator responsiveness (rBDR) in patients with asthma receiving maintenance therapy.
METHODS: In 248 adults with moderate-to-severe asthma receiving inhaled corticosteroids, with or without long-acting bronchodilators, rBDR was assessed according to European Respiratory Society / American Thoracic Society 2005 and 2022 criteria. Maintenance therapy was continued, while short-acting bronchodilators were withheld for at least 12 hours before spirometry. Type 2 biomarkers, lung function including small

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Abbreviations used
ACT- Asthma Control Test
BDR- bronchodilator responsiveness
ERS/ATS- European Respiratory Society / American Thoracic Society
FENO- fractional exhaled nitric oxide
FVC- forced vital capacity
IRR- incidence rate ratio
LABA- long-acting β_2-agonist
LAMA- long-acting muscarinic antagonist
rBDR- residual bronchodilator responsiveness
T2- type 2

airway function, patient-reported outcomes, and exacerbation rates were analyzed according to rBDR status.
RESULTS: rBDR was present in approximately 23% of patients and was consistent across both European Respiratory Society / American Thoracic Society criteria. Maintenance therapy did not differ by rBDR status. Patients with rBDR had higher type 2 biomarkers, despite high-dose inhaled corticosteroid, including sputum eosinophils and fractional exhaled nitric oxide, more frequent fixed airflow obstruction, and greater small airway dysfunction. They also exhibited increased clinical disease burden, with poorer asthma control and frequent exacerbations, independent of underlying lung function and type 2 inflammation.
CONCLUSIONS: rBDR is frequent and identifies patients with refractory type 2 inflammation and poor disease control. rBDR integrates inflammatory activity and functional impairment into a simple, widely available measure and may serve as a practical marker to identify residual disease burden and guide treatment optimization in routine clinical care. **(J Allergy Clin Immunol Pract 2026;■:■-■)**

Key words: *Bronchodilator responsiveness; Asthma; Airway obstruction; Spirometry; Lung function variability; Type 2 inflammation; ERS/ATS criteria; Small airway disease*

INTRODUCTION

Asthma is a chronic inflammatory airway disease characterized by variable symptoms and variable lung function.[1] Among the physiological markers of lung function variability, bronchodilator responsiveness (BDR) is one of the most widely used.[2] By assessing lung function (spirometry) before and after the administration of a short-acting bronchodilator, BDR reflects the reversible component of airflow limitation.[3] Physiologically, it captures the integrated response of airway smooth muscle tone, inflammatory processes, neural regulation, and structural airway properties that together determine airflow.[3]

BDR has traditionally been considered a hallmark in asthma diagnosis in subjects with a clinical picture consistent with asthma.[1,2] However, BDR is not specific to asthma and is frequently observed in other airway diseases such as chronic obstructive pulmonary disease, challenging its role in differentiating between chronic airway diseases.[4-6] Rather than reflecting a disease label, BDR may represent a broader physiological state of airway variability, potentially driven by active inflammation, ongoing exposure to triggers, or insufficient treatment.[2,6,7]

Classically, BDR is assessed at time of asthma diagnosis (before inhaled therapy) or after withholding asthma therapy, particularly long- and short-acting bronchodilators.[3,8] In contrast, residual bronchodilator responsiveness (rBDR) that might be observed despite established maintenance treatment remains poorly understood. In this study, we hypothesized that BDR persisting despite maintenance therapy (rBDR) is associated with ongoing smooth muscle dysfunction and airway inflammation. Accordingly, we aimed to (1) determine the frequency of rBDR in patients with asthma assessed under maintenance treatment, including inhaled corticosteroids, long-acting bronchodilators, and systemic therapies; (2) investigate its relationship with markers of type 2 (T2) inflammation, including blood and sputum eosinophils and fractional exhaled nitric oxide (FENO); and (3) examine its association with clinical features of severe or uncontrolled asthma, including fixed airflow obstruction, small airway dysfunction, patient-reported outcomes of asthma control and quality of life, and exacerbation frequency in adults with asthma. In addition, we applied both the 2005 and 2022 definitions of BDR to evaluate the consistency and clinical relevance of these definitions in identifying residual airway variability.

METHODS

Study design and population

We analyzed baseline data from adults with moderate-to-severe asthma participating in the multicenter, prospective All Age Asthma Cohort (ALLIANCE), a longitudinal observational cohort of pediatric and adult patients with asthma established by the

activities, and editorial work from Vertex Pharmaceuticals, Chiesi, Hogrefe Publishing, StreamedUp, and Philipps University Marburg; and travel support from Vertex Pharmaceuticals; and holds unpaid leadership roles in the German cystic fibrosis Patient Advocacy Board, the German CF Clinical Trial Network Executive Committee, and the European Cystic Fibrosis Society Clinical Trials Network (ECFS-CTN) Executive Committee. K. F. Rabe reports consulting fees from AstraZeneca, Boehringer Ingelheim, Chiesi, and Sanofi & Regeneron; honoraria for lectures and educational activities from AstraZeneca, Boehringer Ingelheim, Chiesi, Sanofi & Regeneron, Berlin Chemie, and Menarini; and participation on advisory boards for AstraZeneca, Boehringer Ingelheim, and Sanofi & Regeneron; and holds leadership roles in the DZL, the German Respiratory Society (DGP), and the American Thoracic Society. B. Schaub reports support for the present study from the DZL and the DFG; consulting fees from GlaxoSmithKline, Novartis, Sanofi, and AstraZeneca; and honoraria for lectures and educational activities from Sanofi, AstraZeneca, and Novartis; and holds a leadership role in the German Society for Allergology and Clinical Immunology (DGAKI). The rest of the authors declare that they have no relevant conflicts of interest.

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German Center for Lung Research (DZL). Details on study design including inclusion and exclusion criteria have been previously published.[9,10] Study visits were performed only in the absence of acute respiratory tract infection or exacerbation within 4 weeks before the visit. The study was approved by the ethics committee at the University of Lübeck School of Medicine (Lübeck, Germany; Az. 21-215) and registered at ClinicalTrials.gov (adult arm: NCT02419274). Written informed consent was obtained from all participants before enrollment.

Bronchodilator responsiveness

rBDR was assessed using spirometry performed before and after the administration of a short-acting bronchodilator. Residual bronchodilation was defined as BDR occurring despite ongoing regular maintenance therapy, including inhaled corticosteroids with or without long-acting bronchodilators, oral corticosteroids, and biologic therapy. Participants were instructed to continue their usual maintenance medication but to withhold short-acting bronchodilators for at least 12 hours before the study visit. Bronchodilation was performed using 400 μg of salbutamol administered via inhalation, and postbronchodilator spirometry was conducted 15 minutes after administration.[11] Patients were classified as responders or nonresponders according to both the 2005 and the 2022 ERS/ATS (European Respiratory Society / American Thoracic Society) criteria. According to the 2005 ERS/ATS criteria, responsiveness was defined as an increase in FEV_1 or forced vital capacity (FVC) of 12% or higher and 200 mL or more from baseline, calculated as the relative change from the prebronchodilator value—(post − pre)/pre × 100.[11] According to the 2022 ERS/ATS criteria, responsiveness was defined as an increase in FEV_1 or FVC of 10% or higher of the predicted value, calculated as ([post − pre]/predicted × 100).[3]

Lung function assessment

Pulmonary function was assessed using spirometry, body plethysmography, and impulse oscillometry in accordance with current ERS standards.[3,12,13] Prebronchodilator and postbronchodilator measurements included FEV_1 (% predicted), FVC (% predicted), and the FEV_1/FVC ratio, using the Global Lung Function Initiative (GLI-2012) reference equations. Postbronchodilator FEV_1/FVC ratios were additionally used to determine the presence of fixed airflow obstruction. Small airway function was evaluated using impulse oscillometry–derived parameters, including the frequency dependence of resistance (R5 − R20) and the reactance area.[14-16] Lung volumes were assessed using the residual volume and total lung capacity.[17]

T2 inflammation markers

T2 inflammation was assessed through blood, induced sputum eosinophil counts, IgE, and FENO. Sputum induction and processing followed standardized operating procedures as we previously described.[18,19]

Medication use and patient-reported outcomes

Medication use was documented, including inhaled corticosteroids, long-acting β_2-agonists (LABAs), long-acting muscarinic antagonists (LAMAs), oral corticosteroids, and biologic therapies, as patient-reported. Asthma control and quality of life were assessed using standardized questionnaires: Asthma Control Test (ACT), 7-item Asthma Control Questionnaire, and Asthma Quality of Life Questionnaire.[20-22]

Statistical analysis

Continuous variables are reported as median (interquartile range), and categorical variables as percentages. For all analyses, the ERS/ATS 2005 and 2022 criteria of BDR were evaluated separately. Between-group comparisons were performed using Wilcoxon rank-sum (Mann-Whitney *U*) tests for continuous variables and χ^2 tests for categorical variables. Associations between outcomes and BDR (rBDR 2005 and rBDR 2022) were evaluated using univariate logistic regression for binary outcomes (odds ratios per 1-SD increase). Negative binomial regression for count outcomes and linear regression for log-transformed continuous outcomes were performed in multivariable models adjusted for age, sex, body mass index, LABA therapy, oral corticosteroid use, LAMA therapy, biologic therapy, fluticasone equivalent dose, and predicted FEV_1. Analyses were conducted in R (version 4.5.0, R Foundation for Statistical Computing, Vienna, Austria) using the packages dplyr, tibble, tidyverse, purrr, broom, MASS, flextable, officer, and ggplot2. A 2-sided *P* value less than .05 was considered statistically significant.

RESULTS

Among 248 patients with asthma, 57 (23.0%) were classified as residual bronchodilator responders according to the 2005 ERS/ATS criteria and 58 (23.4%) according to the 2022 criteria. Median rBDR differed slightly between definitions. When applying the 2005 ERS/ATS criteria (baseline reference), median rBDR was 6.1% (95% CI, 4.7-7.1) for FEV_1 and 2.3% (1.5-2.8) for FVC. When applying the 2022 ERS/ATS criteria (predicted reference), median rBDR was 4.6% (3.8-5.5) for FEV_1 and 2.3% (1.6-2.9) for FVC. Agreement between definitions was high, with Cohen's Kappa of 0.78 (95% CI, 0.69-0.88; $P < .0001$). Of 248 patients, 181 patients were classified as nonresponders by both criteria and 48 as responders. Ten patients were responders only according to the 2005 criteria, whereas 9 were responders only according to the 2022 criteria. Among the 36 patients receiving biologic therapy, 10 (27.8%) were residual bronchodilator responders, with consistent results across both the 2005 and 2022 ERS/ATS criteria.

Baseline characteristics, including age, sex, body mass index, smoking history, and asthma onset, were similar between responders and nonresponders across the 2 BDR definitions (Table I). All patients received inhaled corticosteroids (median fluticasone-equivalent dose 500 μg/d). Most patients (>80%) were additionally treated with LABAs, approximately one-third received LAMAs, about 25% received oral corticosteroids, and 17% received biologic therapy. Maintenance therapies did not significantly differ between responders and nonresponders (Table I).

Responders, defined as patients with a positive rBDR according to either criterion, had more impaired lung function than nonresponders (Table I). Prebronchodilator FEV_1 and FEV_1/FVC were significantly lower in responders, and although the difference was attenuated after bronchodilation, postbronchodilator FEV_1 and FEV_1/FVC remained lower compared with the values in nonresponders. In addition, responders demonstrated more pronounced small airway dysfunction, indicated by higher oscillometry-derived measures of resistance and reactance, as well as higher residual volume / total lung capacity, indicating greater air trapping (Table I).

TABLE I. Baseline characteristics of bronchodilator responders and nonresponders according to the 2005 and 2022 ERS/ATS criteria

	rBDR 2005		rBDR 2022	
Variable	**Responder (n = 57)**	**Nonresponder (n = 191)**	**Responder (n = 58)**	**Nonresponder (n = 190)**
Age (y)	52 (44-59)	52 (44-64)	53 (44-61)	52 (43-63)
Sex (% female)	56.1%	57.1%	58.6%	56.3%
BMI (kg/m^2)	26.5 (23.8-30.5)	27.2 (24.2-30.5)	27.5 (23.9-30.8)	27.1 (24.1-30.1)
Ever smoker	49.1%	51.3%	51.7%	50.5%
Pack-years	5 (2-14)	9 (4-20)	5 (2-13)	9 (5-21)
Early-onset asthma (≤12 y)	22.8%	27.9%	25.9%	27.0%
Late-onset asthma (≥40 y)	31.6%	31.6%	31.0%	31.7%
Fluticasone equivalent (μg)	500 (400-1000)	500 (400-1000)	500 (400-1000)	500 (400-1000)
LABA therapy	84.2%	85.3%	81.0%	86.3%
LAMA therapy	40.4%	29.8%	36.2%	31.1%
Oral corticosteroids	31.6%	23.6%	29.3%	24.2%
Biologic therapy	17.5%	13.6%	17.2%	13.7%
Pre-BD FEV_1 (% predicted)	63 (53-75)	84 (68-99)*	70 (57.25-79)	84 (64-98)*
Pre-BD FVC (% predicted)	93 (85-104)	105 (93-114)*	98 (90-112)	104 (91-113)
Pre-BD FEV_1/FVC	57.6 (49.1-64.9)	68.0 (56.3-74.1)*	58.9 (50.4-65.5)	68.0 (55.6-74.1)*
Post-BD FEV_1 (% predicted)	76.7 (64.11-90.2)	88.5 (71.4-102.1)†	80.1 (68.9-95.6)	86.7 (70.9-100.4)
Post-BD FVC (% predicted)	102.6 (92.6-114.7)	106.9 (94.9-117.0)	107.4 (96.7-120.9)	104.8 (92.9-114.8)
Post-BD FEV_1/FVC	63.0 (52.8-68.0)	69.3 (57.7-76.7)†	63.2 (55.1-68.5)	69.3 (57.1-76.7)‡
IOS R5 − R20 (kPa · s/L)	0.2 (0.1-0.3)	0.1 (0.1-0.2)†	0.2 (0.1-0.3)	0.1 (0.1-0.2)‡
IOS AX (kPa · s/L)	1.3 (0.7-2.9)	0.6 (0.3-1.8)†	1.1 (0.4-2.9)	0.6 (0.3-1.9)‡
IOS Fres (Hz)	20.7 (17.1-26.7)	15.6 (11.9-21.5)*	19.8 (13.1-25.8)	16.7 (12.4-21.6)‡
RV/TLC	44.0 (37.1-49.7)	38.0 (32.6-45.7)†	42.1 (37.0-49.5)	38.8 (32.6-46.0)†
ACT Score	17 (11-21)	19 (14-22)†	16 (10-19)	19 (14-22)†
AQLQ Score	4.8 (3.8-5.7)	5.3 (4.1-6.1)‡	4.62 (3.7-5.6)	5.4 (4.2-6.1)†
ACQ-7 Score	2.6 (1.6-3.3)	1.4 (0.7-2.8)*	2.6 (1.3-3.3)	1.4 (0.7-2.6)*
Exacerbation frequency	2 (0-5)	1 (0-3)‡	2 (0-5)	1 (0-3)‡
Total IgE (kU/L)	175 (47-352)	141 (52-368)	175 (50-349)	141 (50-376)

ACQ-7, 7-Item Asthma Control Questionnaire; *AQLQ*, Asthma Quality of Life Questionnaire; *AX*, reactance area; *BD*, bronchodilator; *BMI*, body mass index; *Fres*, resonant frequency; *ICS*, inhaled corticosteroid; *IOS*, impulse oscillometry; *OCS*, oral corticosteroid; *R5 − R20*, small airway resistance; *RV/TLC*, residual volume to total lung capacity ratio.

Exacerbation frequency, number of severe exacerbations in the previous 12 mo. Continuous variables are presented as median (interquartile range), and categorical variables as percentages. *P* values were calculated using the Wilcoxon rank-sum test for continuous variables and the χ^2 test for categorical variables.

*Statistical significance was defined as $P < .001$.

†Statistical significance was defined as $P < .01$.

‡Statistical significance was defined as $P < .05$.

Furthermore, responders exhibited higher T2 markers than nonresponders (Figure 1). FENO was significantly elevated in responders according to both rBDR definitions. Sputum eosinophils were significantly higher in responders defined by the 2005 rBDR criteria and showed a similar trend under the 2022 definition ($P = .067$). Blood eosinophils were also numerically higher in responders but did not reach statistical significance. In contrast, total serum IgE did not differ between responders and nonresponders according to either criterion (Table I).

Asthma control and quality of life were consistently worse in responders, as reflected by all patient-reported outcome measures (ACT, 7-item Asthma Control Questionnaire, and Asthma Quality of Life Questionnaire) (Table I). In addition, exacerbation frequency in the previous 12 months was higher in responders according to both rBDR criteria. In univariate analyses (Figure 2), better asthma control and higher asthma-related quality of life were associated with lower odds of BDR. A 1-SD increase in the ACT score (5.44 points) was associated with 34% and 40% lower odds of rBDR according to the 2005 and 2022 criteria, respectively. Similarly, a 1-SD increase in the Asthma Quality of Life Questionnaire score (1.27 points) was associated with 29% and 35% lower odds of rBDR, respectively. In contrast, worse asthma control was associated with higher odds of responsiveness. A 1-SD increase in the 7-item Asthma Control Questionnaire score (1.25 points) was associated with 68% and 75% higher odds of rBDR, respectively. Likewise, each 1-SD increase in exacerbation frequency (3.27 events) increased the odds of rBDR by 37% and 39% under the 2005 and 2022 definitions, respectively (Figure 2).

Furthermore, in multivariable analyses, rBDR remained significant with all outcomes after adjustment for demographics, treatment, and baseline FEV_1 (Table II). Higher rBDR was independently associated with markers of higher type 2 inflammation, particularly sputum eosinophils, whereas the association with FENO was weaker but still positive. In addition, higher rBDR was associated with poorer asthma control, as reflected by ACT and Asthma Control Questionnaire scores, and with higher frequency of exacerbations. Moreover, higher rBDR was associated with markers of impaired lung function,

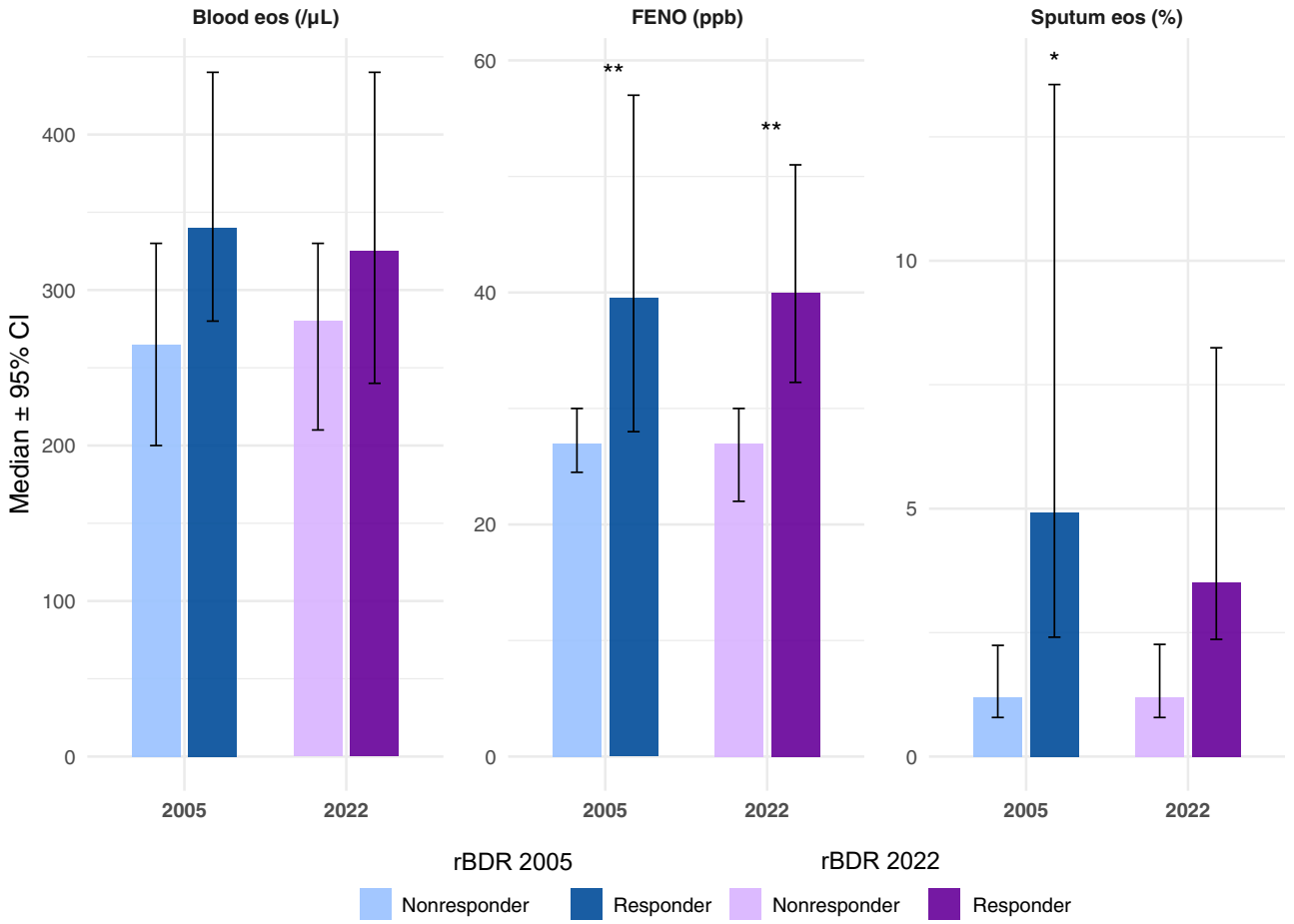

FIGURE 1. Median levels of T2 inflammation markers stratified by BDR definitions (rBDR 2005 vs rBDR 2022). *eos,* Eosinophils; *ppb,* parts per billion. Bars represent the median; error bars indicate 95% bootstrap CI. Significance between groups was assessed using the Mann-Whitney *U* test. Significance between responders and nonresponders is indicated by **P* less than .05 and ***P* less than .01.

including fixed airflow obstruction and small airway dysfunction (Table II).

DISCUSSION

BDR is a key functional marker used to support the diagnosis of asthma; however, the frequency and clinical relevance of rBDR under maintenance therapy have previously been unexplored. In the ALLIANCE cohort, approximately one-quarter of adult patients with moderate-to-severe asthma exhibited rBDR despite established maintenance treatment. The frequency of rBDR was similar when applying the 2005 and 2022 ERS/ATS criteria, with high concordance between definitions. rBDR was independently associated with refractory T2 airway inflammation and lung function limitations, including both small airway dysfunction and airflow obstruction, as well as frequent exacerbations, poor symptom control, and impaired quality of life. Importantly, our study demonstrates that rBDR is clinically meaningful and represents a simple and readily available global marker of insufficient treatment.

The observed frequency of rBDR and the high concordance between 2005 and 2022 ERS/ATS definitions are consistent with prior literature, while providing important clinical context. Previous studies have reported comparable BDR rates of 19% to 30% in a large asthma cohort,[5] whereas others have described higher frequencies of 30% to 42%.[23,24] Notably, these studies assessed BDR after withholding short- and long-acting bronchodilator therapy, an approach expected to unmask greater reversibility. In contrast, our findings demonstrate that a considerable proportion of patients exhibit rBDR despite ongoing treatment, thereby identifying a clinically relevant subgroup with persistent airway reversibility under maintenance treatment.

In our study, patients with rBDR exhibited consistently higher levels of T2 inflammatory markers, with significantly elevated FENO and sputum eosinophils in responders compared with nonresponders, and numerically higher blood eosinophils. These findings were consistent across both ERS/ATS definitions, and multivariable models showed an independent association between T2 markers and rBDR after adjustment for treatment intensity, including bronchodilators (LAMA/LABA), inhaled corticosteroid dose, systemic corticosteroid use, and biologic therapy.

Notably, patients with rBDR were predominantly treated with medium- to high-dose inhaled corticosteroids, yet continued to exhibit elevated T2 markers, consistent with the concept of refractory T2 inflammation as proposed by the Global Initiative for Asthma.[2] Our observations suggest that

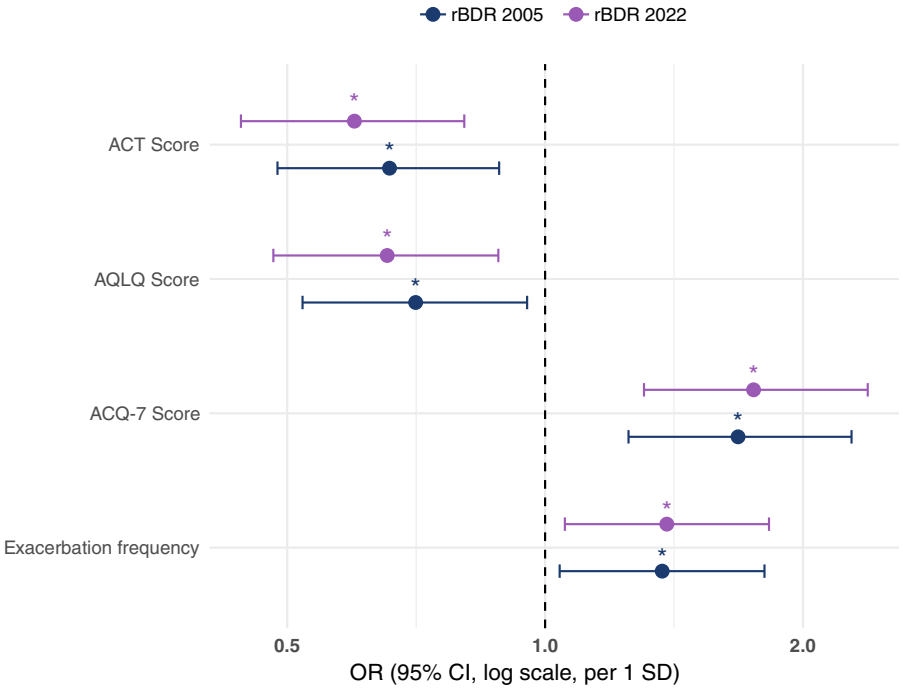

FIGURE 2. Univariate ORs per 1-SD increase for asthma quality-of-life and symptom scores for BDR according to the 2005 and 2022 ERS/ATS criteria. *ACQ-7*, 7-Item Asthma Control Questionnaire; *OR*, odds ratio; *rBDR 2005*, relative change from baseline according to the 2005 ERS/ATS criteria; *rBDR 2022*, relative change from predicted according to the 2022 ERS/ATS criteria; *SAD*, Small airways dysfunction. Points represent ORs, and horizontal lines indicate 95% CI. Statistical significance is indicated by *P* less than .05. OR more than 1 indicates higher odds of being a bronchodilator responder. Univariate ORs per 1-SD increase for asthma clinical variables for BDR according to the 2005 and 2022 ERS/ATS criteria.

rBDR reflects persistent inflammatory activity despite ongoing therapy. Physiologically, BDR captures the integrated response of airway smooth muscle, inflammatory mediators, neural regulation, and structural airway properties that collectively determine airflow limitation.[3] Restoration of airway smooth muscle function is closely linked to improved asthma control and overall airway health, reflecting the central role of airway remodeling in disease severity and exacerbation risk.[25] Importantly, airway inflammation and airway smooth muscle dysfunction are closely interconnected, because inflammatory mediators such as IL-4, IL-5, and IL-13 directly regulate smooth muscle proliferation, contractility, and hyperresponsiveness.[26,27] In this context, T2 biomarkers reflect local airway inflammatory activity and are well-established predictors of corticosteroid responsiveness,[28,29] while sputum eosinophils and FENO have also been associated with overall disease burden in severe asthma.[30,31] Consistent with this framework, previous studies have shown that reduced or absent BDR is associated with T2-low asthma phenotype[32] and lower FENO levels,[23] further supporting a link between BDR and underlying T2 inflammatory activity. Whether rBDR is modifiable by T2-targeted biologic therapy remains unknown. Given the association of rBDR with persistent T2 inflammatory activity, effective suppression of T2 inflammation may reduce or abolish rBDR; however, the small number of patients receiving biologics and the cross-sectional design of the present study preclude assessment of this hypothesis. Future longitudinal studies should determine whether diminishing rBDR following initiation of T2-targeted biologic therapy reflects a global treatment response, including improvements in T2 biomarkers, asthma control, exacerbation risk, and lung function.

Beyond its association with T2 inflammation, rBDR was consistently linked to more pronounced impairment in lung function, including both airflow obstruction and small airway dysfunction. This finding closes an important conceptual loop: rBDR under maintenance therapy reflects continued disease activity, characterized by persistent T2 inflammation and its functional consequences on the airways. Notably, the association with small airway dysfunction remained independent of demographics, treatment, and baseline FEV_1, underscoring its robustness. Previous studies have demonstrated a close relationship between T2 inflammation and lung function impairment, particularly at the level of the small airways,[19,33] which are increasingly recognized as key contributors to asthma severity, symptom burden, and T2 inflammation.[33] Importantly, small airway dysfunction and airflow obstruction frequently coexist but represent distinct and only partially overlapping domains,[34] with dynamic changes in T2 inflammatory activity being more sensitively reflected by measures of small airway function than by FEV_1.[19] In line with this, therapeutic studies have shown that targeting T2 inflammation reduces exacerbations and improves outcomes, with treatment response better predicted by functional markers beyond classical spirometry. For example, the benefit of omalizumab on exacerbation risk has been linked to BDR rather than baseline airflow obstruction,[35] while clinical response to anti—IL-5 biologics is better predicted by small airway resistance than by

TABLE II. Associations of rBDR according to the 2005 and 2022 definitions with T2 inflammation, asthma control, exacerbations, fixed airflow obstruction, and small airway disease

Outcome	Predictor	Estimate (95% CI)	*P* value
T2 inflammation (sputum eos ≥2)	rBDR 2005	OR 1.79 (1.24-2.65)	.002
	rBDR 2022	OR 1.45 (1.05-2.04)	.027
T2 inflammation (FENO ppb)	rBDR 2005	β 0.14 (0.04-0.24)	.005
	rBDR 2022	β 0.14 (0.05-0.24)	.004
Exacerbation frequency	rBDR 2005	IRR 1.25 (1.07-1.45)	.004
	rBDR 2022	IRR 1.29 (1.11-1.5)	.001
ACT Score (<20)	rBDR 2005	OR 1.37 (1.02-1.85)	.038
	rBDR 2022	OR 1.6 (1.19-2.19)	.003
ACQ Score (≥1.5)	rBDR 2005	OR 1.79 (1.31-2.49)	<.001
	rBDR 2022	OR 1.72 (1.27-2.38)	.001
Fixed airflow obstruction ($FEV_1/FVC < 0.7$)	rBDR 2005	OR 1.71 (1.23-2.44)	.002
	rBDR 2022	OR 1.74 (1.25-2.48)	.001
SAD AX (>1.0 kPa · L)	rBDR 2005	OR 1.39 (1.03-1.88)	<.05
	rBDR 2022	OR 0.13 (0.06-0.19)	<.001
SAD AX (kPa · L)	rBDR 2005	β 0.13 (0.06-0.19)	<.001
	rBDR 2022	β 0.09 (0.03-0.15)	<.01
SAD R5 − R20 (>0.07 kPa · s/L)	rBDR 2005	OR 1.87 (1.33-2.75)	.001
	rBDR 2022	OR 1.34 (0.98-1.88)	.072
SAD R5 − R20 (kPa · s/L)	rBDR 2005	β 0.02 (0.01-0.03)	<.01
	rBDR 2022	β 0.01 (0.00-0.03)	<.05
SAD RV/TLC ≥40%	rBDR 2005	OR 1.58 (1.15-2.23)	<.01
	rBDR 2022	OR 1.34 (0.98-1.85)	.066
RV/TLC (%)	rBDR 2005	β 0.05 (0.03-0.07)	<.001
	rBDR 2022	β 0.04 (0.02-0.06)	<.001

ACQ, Asthma Control Questionnaire; *AX*, reactance area; *eos*, eosinophil; *IRR*, incidence rate ratio; *OR*, odds ratio; *ppb*, parts per billion; *R5 − R20*, small airway resistance; *RV/TLC*, residual volume to total lung capacity ratio; *SAD*, small airway dysfunction.
Values are ORs, IRRs, or β coefficients with 95% CI. Logistic regression was used for binary outcomes, negative binomial regression for count outcomes, and linear regression for log-transformed continuous outcomes; models were adjusted for age, sex, BMI, LABAs, oral corticosteroids, LAMAs, biologics, inhaled corticosteroid dose, and predicted FEV_1; statistical significance is indicated by *P* values.

FEV_1.[36] Together, these findings suggest that rBDR captures the active, potentially reversible component of airway disease, whereas persistent airflow obstruction may increasingly reflect cumulative, less reversible airway remodeling. In this context, rBDR may serve as a functional marker of the window of reversibility, identifying patients in whom ongoing inflammatory activity continues to drive modifiable airway dysfunction before fixed impairment becomes established.[25]

Furthermore, rBDR was consistently associated with worse clinical outcomes, including poorer asthma control, lower asthma-related quality of life, and more frequent exacerbations. These associations remained significant after adjustment for baseline lung function and treatment, indicating that rBDR identifies a subgroup of patients with inadequate asthma control despite ongoing maintenance therapy. In line with previous work, increased BDR has been proposed as a functional marker of airway instability and heightened susceptibility to exacerbations.[25,37] In contrast, Kaminsky et al[24] reported no association between BDR and asthma control or symptoms; however, their analysis was based on assessments performed after withholding maintenance therapy across different study settings. This distinction is critical, because withdrawal of anti-inflammatory and bronchodilator treatment might transiently unmask reversibility, whereas our approach captures rBDR under treated conditions.

The 2005 and 2022 ERS/ATS criteria showed a substantial overlap in the patients classified by each definition, indicating that rBDR is a stable and robust feature in established asthma. Despite minor differences in baseline lung function, clinical outcomes, including symptom burden, asthma control, quality of life, and exacerbation risk, were consistent between definitions. These findings suggest that the updated criteria provide refinement in functional phenotyping without altering the clinical relevance of rBDR or its ability to identify patients at risk for poor outcomes.[38]

Limitations

Limitations of this study include its observational design, which precludes causal inference. BDR was assessed at a single time point, and therefore intraindividual variability in rBDR over time could not be captured; however, the longitudinal design of the ALLIANCE cohort will allow future evaluation of its temporal stability and dynamics. Although analyses were adjusted for treatment intensity, treatment patterns likely reflect underlying disease severity, which may influence the observed associations. In addition, the cohort predominantly comprised patients with moderate-to-severe asthma, which may limit generalizability to milder disease.

Conclusion

Our findings demonstrate that rBDR is frequent and clinically meaningful in patients with asthma despite ongoing maintenance therapy. rBDR identifies a subgroup with active, insufficiently

controlled disease, characterized by refractory T2 inflammation, impaired lung function, including small airway dysfunction, and an increased burden of symptoms and exacerbations. Although bronchodilator testing is traditionally performed after withholding therapy for diagnostic purposes, our results highlight that assessment under continued treatment may provide actionable clinical information. In routine care, the presence of rBDR should therefore be interpreted as a marker of inadequate disease control that might guide treatment optimization. However, confirmatory evidence regarding its role in guiding treatment decisions will require longitudinal and interventional studies.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE MANUSCRIPT PREPARATION PROCESS

During the preparation of this work, the authors used ChatGPT to check for writing, grammar, and formulation of language. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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