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ORIGINAL RESEARCH

Assessment of Bronchodilator Responsiveness and Spirometric Patterns in Patients with Rhinitis and Suspected Asthma

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Background: Bronchodilation testing (BDT) is routinely used to assess reversibility of airflow limitation. For patients with rhinitis who report asthma-related symptoms but often show preserved spirometry, the clinical patterns associated with bronchodilator responsiveness (BDR) are less clearly described. Understanding these patterns may help clinicians interpret lung function in real-world practice.

Methods: We retrospectively analyzed 555 consecutive patients who underwent spirometry and BDT at a single tertiary allergy center. Data on clinical symptoms, allergic status, type-2 inflammatory markers, baseline spirometry results, and BDT outcomes were collected. Associations between symptoms, spirometric indices, and BDR were evaluated. Exploratory analyses examined the relationship between FEV_1 improvements below the conventional ≥12% criterion and asthma-related symptoms.

Results: Among all participants, 71.9% had allergic rhinitis, and 88.6% reported asthma-related symptoms. BDR was observed across a wide range of baseline spirometry values; 47.2% of BDT-positive patients had FEV_1 ≥80% predicted. Small airway indices, especially FEF_{50} % predicted, were strongly associated with BDR. Wheezing and chest tightness demonstrated clearer physiological correlations than coughing alone did. FEV_1 improvements slightly below the conventional ≥12% bronchodilator threshold were also associated with asthma-related symptoms, although these findings were exploratory and not intended as diagnostic criteria.

Conclusion: In patients with rhinitis and suspected asthma, airflow variability may be present even when FEV_1 appears preserved. Small-airway parameters and symptom profiles offer a useful context for interpreting BDT results. Modest FEV_1 changes may be clinically relevant and warrant further prospective study. These findings may help clinicians judge when bronchodilation testing is informative during the routine evaluation of suspected airway disease.

Keywords: bronchodilator responsiveness, spirometry, rhinitis, asthma, small-airway function, airflow variability

Introduction

Asthma is a common bronchial disease characterized by chronic airway inflammation and bronchial hyperresponsiveness, affecting 6.2% of children and 8.7% of adults worldwide, but regional variations should be considered when interpreting these estimates.[1] Although the prevalence and incidence of asthma have stabilized or even declined in some regions, its prevalence in mainland China has continued to rise over the past three decades.[2] Asthma imposes a substantial health and economic burden worldwide, including emergency visits, hospitalizations, and deaths.[3,4] Atopy and allergic rhinitis (AR) are important predisposing factors of asthma.[5–9] Currently, rhinitis and asthma are closely related diseases with common physiological and inflammatory mechanisms in the upper and lower airways.[10] There is a great deal of overlap between the two diseases; over 80% of patients with asthma have rhinitis, and 10%-40% of those with rhinitis develop asthma.[11] Both can be divided into allergic and non-allergic rhinitis or asthma, with

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different mechanisms and features.[12,13] Prior studies have also suggested subclinical airflow limitation in children with AR and highlighted FEF_{25-75} as a potential early marker of lower airway involvement.[14]

Early diagnosis is essential for the management and prognosis of asthma,[15,16] requiring the integrating of symptoms, examination, and clinical history. Bronchodilation test (BDT) is a guideline-endorsed tool.[17,18] The ≥12% (and 200 mL) FEV_1 threshold was derived from studies in patients with clinically confirmed asthma.[19,20] However, its performance may vary when applied in clinical practice, particularly in patients with asthma-like symptoms but near-normal baseline spirometry.[21] For patients with suspected asthma but normal spirometry, some experts recommend performing BDT first,[22] whereas others advocate proceeding directly to bronchial provocation testing (BPT).[23] Although BPT is widely used in diagnostic evaluation, it is more complex and time-consuming to perform, may incur higher costs, and its interpretation can vary depending on the provoking agents used (eg, methacholine, histamine, mannitol, or hyperventilation). The Chinese consensus allows BPT when FEV_1 >70%, but—unlike international practice—does not explicitly require that BPT be used only after non-provocative tests such as BDT remain non-diagnostic.[24] In routine clinical practice, BDT may already be sufficient to identify reversible airflow limitation in a subset of patients with rhinitis and asthma-like symptoms, without the immediate need for BPT. Although BPT is generally safe under standardized protocols, emerging mechanistic evidence suggests that bronchoconstriction itself may injure the airway epithelium via crowding-induced cell extrusion, with potential human relevance,[25] highlighting the importance of carefully selecting patients for BPT whenever possible.

Accumulating evidence indicates that conventional BDT criteria may perform sub-optimally in patients with AR. Many patients with AR report asthma-like symptoms despite preserved baseline spirometry; therefore, reversible airflow limitation may be under-recognized when the assessment relies primarily on baseline obstruction. Several studies have proposed lower FEV_1 improvement thresholds, such as 7.5%, 9%, or 10%, to increase sensitivity,[26–28] whereas others have explored the role of small-airway indices as early indicators of airway involvement.[29–31] However, how these spirometric features relate to respiratory symptoms and type 2 inflammatory markers in real-world rhinitis-predominant populations remains unclear.

In this study, we evaluated spirometry and bronchodilator responsiveness (BDR) in a real-world cohort predominantly composed of patients with rhinitis and examined their relationship with respiratory symptoms and type 2 inflammatory indicators, with the aim of providing practical, symptom-informed insights into the interpretation of bronchodilation testing in routine clinical evaluations in everyday clinical practice.

Methods

Study Design and Population

This retrospective observational cohort study enrolled consecutive patients attending a tertiary allergy center (Department of Allergy, Peking Union Medical College Hospital) who underwent spirometry and BDT for suspected asthma or follow-up between March and November 2022. Eligible participants were aged ≥4 years with or without atopy and rhinitis. Both pediatric and adult patients were included to reflect the real-world clinical population undergoing spirometry and bronchodilator testing in an allergy specialty center. Exclusion criteria included acute pulmonary infection within 4 weeks, history of lung surgery, or severe comorbid conditions including cardiovascular and cerebrovascular disease, malignancy, or autoimmune disease. An independent reference diagnosis of asthma, separate from spirometry or BDT, was not uniformly applied across the cohort. Instead, physician diagnoses at the time of referral were recorded. Participants without typical asthma-related symptoms at the time of testing were described as the internal comparator group.

This study was approved by the Ethical Committee of Peking Union Medical College Hospital (No. I-23PJ573). Given the retrospective and observational nature of the study, which involved analysis of anonymized clinical data collected during routine care without additional interventions, the requirement for written informed consent was waived by the Ethics Committee. The study included both adult and pediatric patients. For minors, the Ethics Committee approved the waiver of informed consent from parents or legal guardians under the same conditions. All procedures were conducted in accordance with the Declaration of Helsinki.

Clinical and Demographic Information Collection

Demographic and clinical data, including sex, age, BMI, suspected asthma symptoms, total IgE (T-IgE), fractional exhaled nitric oxide (FeNO), and blood eosinophil counts/proportion, were collected. Rhinitis was diagnosed by experienced allergists based on a clinical history of sneezing, a runny nose, or a blocked nose in the absence of a cold or the flu.[32] Allergic rhinitis was defined as meeting the diagnostic criteria for rhinitis, and at least one allergen-specific IgE (sIgE) ≥0.35 kU/L. Non-allergic rhinitis was defined as meeting the diagnostic criteria for rhinitis, but with negative sIgE to common aeroallergens. Atopy was defined as positive sIgE sensitization. We recorded the physician's diagnoses and documented respiratory symptoms at the time of spirometry/BDT. The suspected asthma symptoms include cough, chest tightness, and wheezing.

Spirometry and BDT

Spirometry was performed on an MIR Spirolab III spirometer (Italy) following standard guidelines.[33] The FEV_1/FVC z-scores were derived from the Global Lung Function Initiative (GLI) reference equations (adjusted for age, sex, and height).[34] BDT was performed according to international guidelines, using salbutamol at a dose of 200 μg. In adults (≥ 18 years), a positive BDT was defined as an increase in FEV_1 of ≥ 12% and ≥200 mL from baseline, whereas in patients <18 years, only an increase of ≥12% was observed.[17,35] In adults, a "suspiciously positive" BDT was defined as meeting only one of the two conventional reversibility criteria—either ≥12% or ≥200 mL improvement in FEV_1. Small airway dysfunction was defined when two or more of FEF_{25-75}, FEF_{50}, and FEF_{75} were <65% predicted and were considered suspicious when only one indicator was <65% predicted.[36] The reversibility of small airways was defined as an increase in FEF_{25-75} ≥30% after BDT.[19]

Statistical Analyses

Demographic and clinical characteristics were compared among ≥3 groups using ANOVA, Kruskal–Wallis tests, Pearson's chi-squared tests, or Fisher's exact tests, as appropriate, followed by post-hoc Tukey's HSD multiple comparisons or Bonferroni-Holm correction to assess differences between groups. Differences in spirometric parameters between the two groups were analyzed using the Wilcoxon rank-sum test, Pearson's chi-squared test, or Fisher's exact test, as appropriate. Pearson's correlation analyses were performed between continuous variables, and T-IgE values were logarithmically transformed because of their skewed distribution. Receiver operating characteristic (ROC) curves were constructed to evaluate the ability of spirometry indices to predict positive BDT results, as well as the ability of percent FEV_1 improvement after BDT to predict highly suspected asthma symptoms (chest tightness and wheezing), with optimal cut-off values determined using the Youden index. A two-sided P-value <0.05 was considered significant. Statistical analyses were performed using R (version 4.3.0) and SPSS (version 24.0; IBM Statistics, Chicago, IL, USA).

Results

Patients Demographics and Clinical Characteristics

A total of 555 patients were enrolled, including 115 children (≤14 ys). The proportion of male patients was higher in children (68.7%) than in adults (35.7%). Of all participants, 399 had allergic rhinitis, 75 had non-allergic rhinitis, 32 had atopy without rhinitis, and 49 had neither. Sex distribution and BMI were comparable among the four groups, whereas patients with allergic rhinitis were significantly younger than those in the non-allergic rhinitis and no atopy or rhinitis groups (P<0.001). Overall, 88.6% of patients reported suspected asthma symptoms, including 68.1% with cough, 59.1% with chest tightness, and 52.0% with wheezing. The remaining 11.4% of patients reported no typical asthma symptoms at the time of testing, served as the internal comparator group. The FeNO levels were higher in allergic patients and lowest in patients without atopy or rhinitis, although no significant differences were observed in pairwise comparisons. T-IgE levels were higher in both atopic groups than in the two non-atopic groups (P<0.001), and also higher in patients with non-allergic rhinitis than in patients without either atopy or rhinitis (P=0.03). Blood eosinophil counts and proportions were higher in patients with allergic rhinitis than in those with non-allergic rhinitis and without atopy or rhinitis (P<0.05). Spirometric indices were largely comparable among the four groups, except for FEV_1/FVC (P=0.01), which was significantly higher in patients with allergic rhinitis than in those without atopy or rhinitis (P=0.03) (Table 1).

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Table 1 Demographic and Clinical Characteristics of Patients in Different Groups

Characteristic	Allergic Rhinitis (n=399)	Non-Allergic Rhinitis (n=75)	Atopy without Rhinitis (n=32)	No Atopy or Rhinitis (n=49)	*P*-value
Male (%)	178 (44.6)	27 (36.0)	13 (40.6)	18 (36.7)	0.43
Age, years, mean (SD)	29.81 (15.94)	40.20 (15.88)	35.81 (20.73)	41.96 (17.93)	<0.001
BMI, kg/m^2, mean (SD)	22.58 (4.33)	23.57 (3.89)	23.07 (5.24)	23.77 (4.36)	0.12
Any suspected asthma symptom (%)	344 (86.4)	72 (96.0)	30 (93.8)	45 (91.8)	0.06
Coughing (%)	256 (67.2)	54 (73.0)	23 (71.9)	32 (65.3)	0.72
Chest tightness (%)	209 (56.0)	49 (69.0)	18 (60.0)	32 (68.1)	0.12
Wheezing (%)	192 (50.9)	43 (60.6)	17 (56.7)	22 (44.9)	0.32
FeNO, ppb, median (IQR)	35 (19–57.5)	22 (10–41)	36 (12.5–73.5)	13 (9–14.75)	0.04
TIgE, kU/L, geometric mean (95% CI)	260 (231–292)	88 (55.7–115)	365 (258–516)	31.6 (21.8–45.9)	<0.001
ESO#, $\times 10^9$/L, median (IQR)	0.32 (0.18–0.57)	0.17 (0.08–0.33)	0.28 (0.17–0.50)	0.15 (0.11–0.23)	<0.001
ESO%, %, median (IQR)	4.7 (2.7–7.5)	2.5 (1.5–6.6)	4.1 (2.8–5.92)	2.6 (1.45–3.9)	0.001
Spirometry					
FEV_1/FVC, %, mean (SD)	80.30 (8.67)	77.80 (9.92)	78.39 (9.67)	76.56 (10.20)	0.01
FEV_1, % predicted, mean (SD)	97.68 (15.62)	97.37 (18.02)	93.50 (19.20)	98.73 (21.23)	0.54
FEV_1/FVC, % predicted, mean (SD)	94.71 (9.41)	94.68 (10.97)	94.31 (10.43)	93.29 (11.48)	0.82
FEF_{25-75}, % predicted, mean (SD)	85.14 (26.20)	85.17 (29.52)	84.25 (33.31)	86.04 (35.99)	0.99
FEF_{50}, % predicted, mean (SD)	73.79 (22.79)	71.77 (25.66)	72.03 (31.92)	69.76 (27.69)	0.67
FEF_{75}, % predicted, mean (SD)	71.46 (26.25)	67.09 (24.54)	68.53 (30.59)	69.27 (32.75)	0.58
FEV_1 post, % predicted, mean (SD)	102.16 (15.73)	102.91 (16.81)	98.69 (20.00)	104.51 (18.18)	0.46
FEF_{25-75} post, % predicted, mean (SD)	97.00 (26.66)	96.36 (29.61)	94.31 (33.82)	99.61 (34.43)	0.86

Abbreviations: BMI, body mass index; ESO, eosinophil; FeNO, fractional exhaled nitric oxide; TIgE, total immunoglobulin E; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEF25-75, forced expiratory flow between 25% and 75% of vital capacity; FEF50, forced expiratory flow at 50% of vital capacity; FEF75, forced expiratory flow at 75% of vital capacity; SD, standard deviation; IQR, interquartile range; post, post-bronchodilator.

Association of Spirometry Results with Suspected Asthma Symptoms

To examine how baseline spirometric indices were associated with asthma-related symptoms, spirometry parameters were compared between patients with and without wheezing, chest tightness, or cough. There was no significant difference in FEV_1 (% predicted) between patients with and without suspected asthma symptoms (Figure 1A), whereas those with symptoms had a lower FEV_1/FVC (P<0.001, Figure 1B) and FEF_{25-75} (% predicted) (P=0.03, Figure 1C). Patients with and without cough showed no difference in FEV_1 (% predicted), FEV_1/FVC or FEF_{25-75} (% predicted) (Figures 1D, S1A and B). In contrast, patients with chest tightness (P<0.01) or wheezing (P<0.001) had significantly lower FEV_1 (% predicted), FEV_1/FVC and FEF_{25-75} (% predicted) than those without these symptoms (Figure 1E and F, S1C–F). Patients with suspected asthma symptoms had larger proportion of small airway reversibility (15.1% vs. 11.1%, P=0.40), as well a larger positive and suspiciously positive proportion of BDT (27.3% vs. 20.6, P=0.26) and small airway dysfunction (53.6% vs. 38.1%, P=0.02), with only the latter reaching statistical significance (Figure 1G–I). Most of patients with positive or suspiciously positive BDT (78.1%) or small airway reversibility (86.3%) also had small airway dysfunction (Figure 1J).

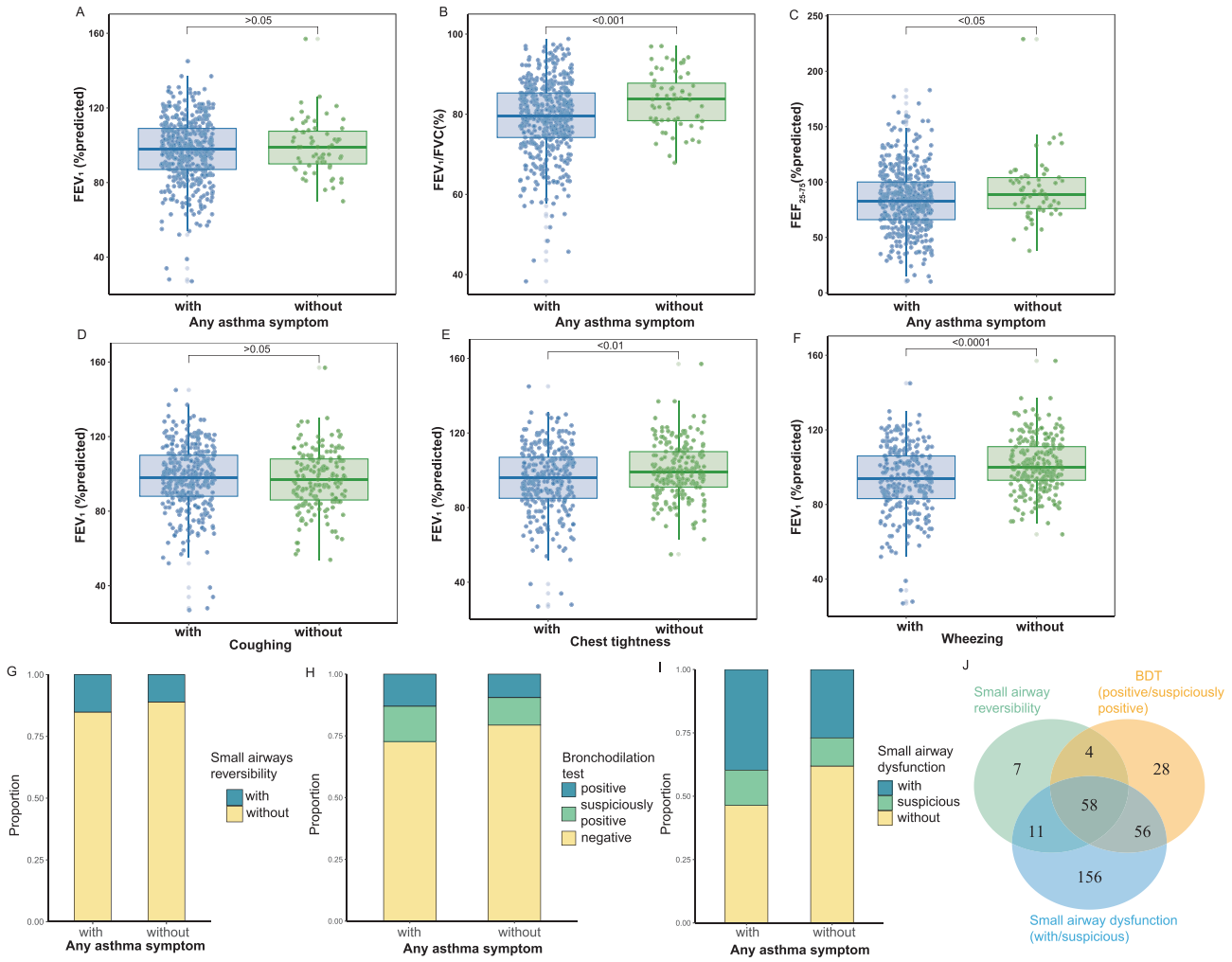

Figure 1 Associations between spirometry parameters and suspected asthma symptoms. (**A–C**) Comparison of FEV_1 (% predicted), FEV_1/FVC, and FEF_{25-75} (% predicted) between patients with and without any suspected asthma symptoms (cough, chest tightness, or wheeze). (**D–F**) Comparison of FEV_1 (% predicted) for each individual symptom—cough (**D**), chest tightness (**E**), and wheeze (**F**) between patients with and without individual symptoms of coughing, chest tightness, and wheezing. (**G–I**) Proportions of small airway reversibility, BDT results, and small airway dysfunction between patients with and without any suspected asthma symptoms. (**J**) Venn diagram showing the overlap among patients with small airway reversibility, positive or suspiciously positive BDT results, and small airway dysfunction. Statistical comparisons were performed using the Wilcoxon test for continuous variables and χ^2 or Fisher's exact test for categorical variables; significance levels (P) are shown above each panel.
Abbreviations: BDT, bronchodilation test; FEF_{25-75}, forced expiratory flow between 25 and 75% of vital capacity; FEV_1, forced expiratory volume in 1s; FVC, forced vital capacity.

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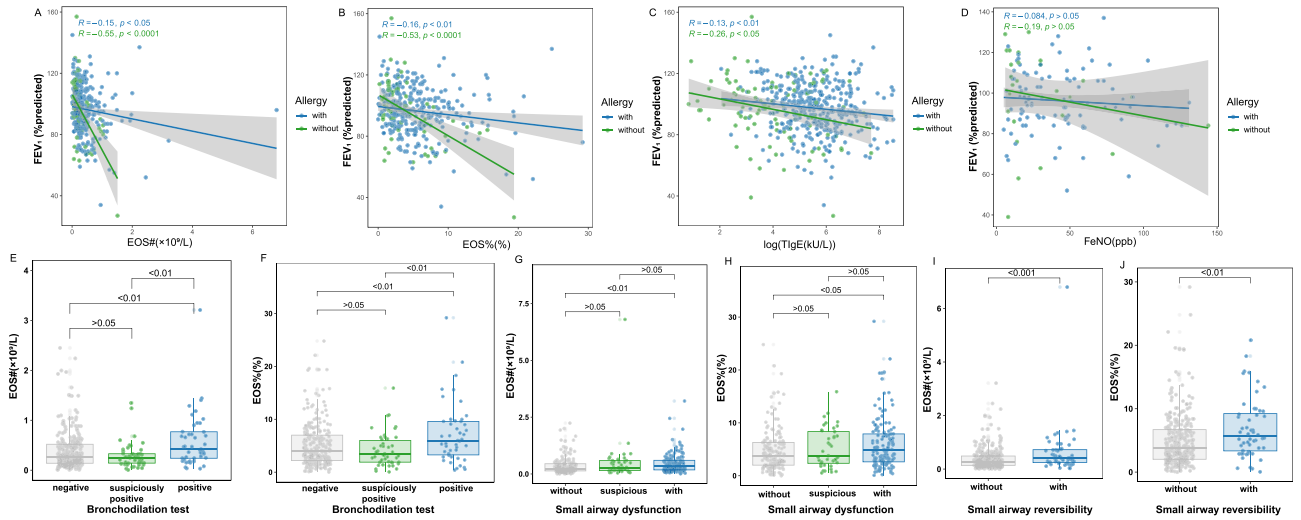

Figure 2 Associations between spirometry results and type 2 inflammation indicators. (**A**–**D**). Correlations of FEV_1 (% predicted) with key type 2 inflammatory biomarkers: (**A**) blood eosinophil counts, (**B**) eosinophil proportion, (**C**) log_{10} (Total IgE), and (**D**) FeNO in patients with and without atopy. Pearson correlation coefficients (R) and P values are shown in each panel. (**E**–**J**) Comparisons of blood eosinophil counts and eosinophil proportion among subgroups defined by (**E** and **F**) small-airway reversibility, (**G** and **H**) BDT outcomes (positive, suspiciously positive, or negative), and (**I** and **J**) small-airway dysfunction. Boxplots depict medians and interquartile ranges; significance was assessed with Mann–Whitney *U*-test.

Abbreviations: BDT, bronchodilation test; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; EOS, eosinophil; TIgE, total immunoglobulin E.

Association of Spirometry Results with Type 2 Inflammation Indicators

To explore the interplay between airway physiology and type-2 inflammation, we further investigated the association between spirometry and markers of type-2 (T2) inflammation (blood eosinophil counts and FeNO) and T-IgE. FEV_1 (% predicted) was negatively correlated with both eosinophil counts (r=−0.19, P<0.001) and proportion (r=−0.23, P<0.001), and the negative correlation trend was especially obvious in non-allergic patients (Figure 2A and B). A weak negative correlation was observed between FEV_1 (% predicted) and log_{10}(T-IgE) (r=−0.15, P=0.002) (Figure 2C). There was a weak and non-significant negative correlation between FEV_1 (% predicted) and FeNO, although the difference was not statistically significant (r=−0.12, P=0.17) (Figure 2D). BDT-positive patients had significantly higher eosinophil counts and proportions compared to BDT suspiciously BDT-positive and BDT-negative patients (P<0.01) (Figure 2E and F). However, there was no significant difference in log_{10}(T-IgE) levels (Figure S2A) and FeNO (Figure S2B) among patients with different BDT results. As for small airways, patients with small airway dysfunction and reversibility had significantly higher eosinophil counts and proportions than patients with normal small airway conditions (P<0.05) (Figure 2G–J), but no significant difference in log_{10}(T-IgE) (Figure S2C and D) and FeNO (Figure S2E and F) were observed.

The Cut-Off Value of Spirometry Indicators to Guide BDT Performing

To identify practical apirometric thresholds that could guide the decision to perform BDT, we evaluated the ability of baseline indices to predict a positive BDT result. While BDT is widely performed in all suspected asthma patients internationally, some Chinese institutions use FEV_1 <80% predicted as a practical indicator for selecting patients for BDT. However, this cut-off value could only identify 52.8% of patients with positive BDT results, whereas FEV_1 (% predicted) < 100% could identify 90.3% of BDT-positive patients (Table 2 and Figure 3A). This high rate of missed diagnoses was observed in allergic and non-allergic patients, as well as in adults and children, while non-allergic patients and children showed a higher ratio of positive BDT results (Figure 3A and B). In addition, using a threshold of FEV1/FVC z-score < −1.645 (the GLI lower limit of normal) identified 80.6% of patients with positive BDT results (Figure S3). ROC curve revealed the predictive value of FEV_1 (% predicted) for BDT positivity with an area under the ROC curve (AUC) of 0.836 (95% CI 0.785–0.887, P<0.001) and a cut-off value to be 92.5% (Figure 3C), indicating moderate discriminative ability of baseline FEV1 in predicting BDR and support using a higher threshold than 80% to better capture at-risk patients. Other spirometry indices, including FEV_1/FVC, FEF_{25-75}, FEF_{50}, FEF_{75} (% predicted), also

Table 2 Sensitivity and Specificity for Different FEV_1 (% Predicted) Cut-off Values to Predict BDT Positive

FEV_1 (% Predicted)	Sensitivity	Specificity	Youden Index
<80%	52.8%	92.3%	0.451
<90%	77.8%	75.4%	0.532
<92.5%	86.1%	73.5%	0.596
<100%	90.3%	47.6%	0.379

Abbreviations: FEV1, forced expiratory volume in 1 second; BDT, bronchodilation test.

showed predictive value for positive BDT by ROC analysis (all $P<0.001$). Among these, FEF_{50} (% predicted) reached the best AUC (0.860, 95% CI 0.810–0.909) with a cut-off value of 58.5% (Figure 3D and S4A–C), suggesting that small-airway parameters may provide additional information related to early bronchial reversibility.

Relationship Between FEV1 Improvement and Respiratory Symptoms

To reassess the diagnostic thresholds for BDR, we analyzed how different FEV_1 improvements corresponded to the symptoms. According to the traditional criteria for BDT, only 13.0% of patients with any suspected asthma symptoms had positive BDT results and would meet conventional criteria for BDR (Figure 1G), which prompted us to reassess the cut-off value of BDT percent improvements. In comparison, we noticed that allergic patients had significantly higher

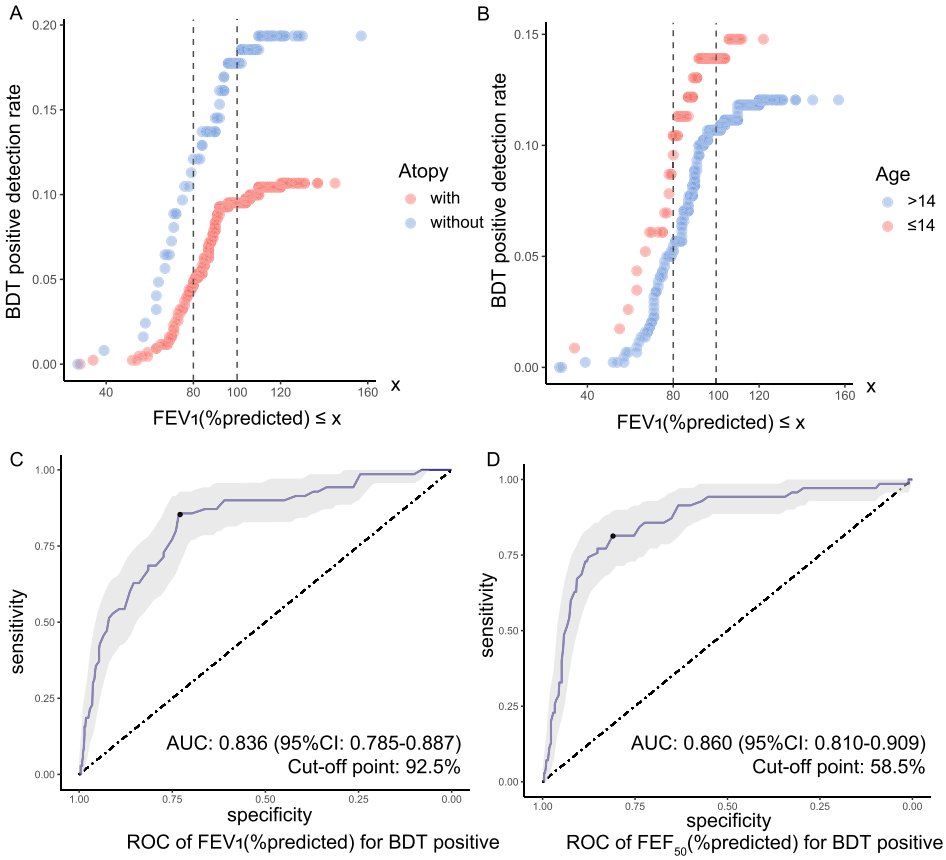

Figure 3 Prediction value of spirometry indicators for identifying patients who should undergo bronchodilation testing. (**A**) Positive detection rates of the BDT at different cut-off values of FEV_1 (% predicted) in patients with and without atopy. (**B**) Positive detection rates of BDT across different cut-off values of FEV_1 (% predicted) in children and adults. (**C** and **D**) ROC curves for FEV_1 (% predicted) and FEF_{50} (% predicted), respectively, in predicting positive BDT results. AUC values with 95% CI and optimal thresholds are indicated.

Abbreviations: AUC, area under the curve; BDT, bronchodilation test; CI, confidence interval; FEV_1, forced expiratory volume in one second; FEF_{50}, forced expiratory flow at 50% of vital capacity; ROC, receiver operating characteristic.

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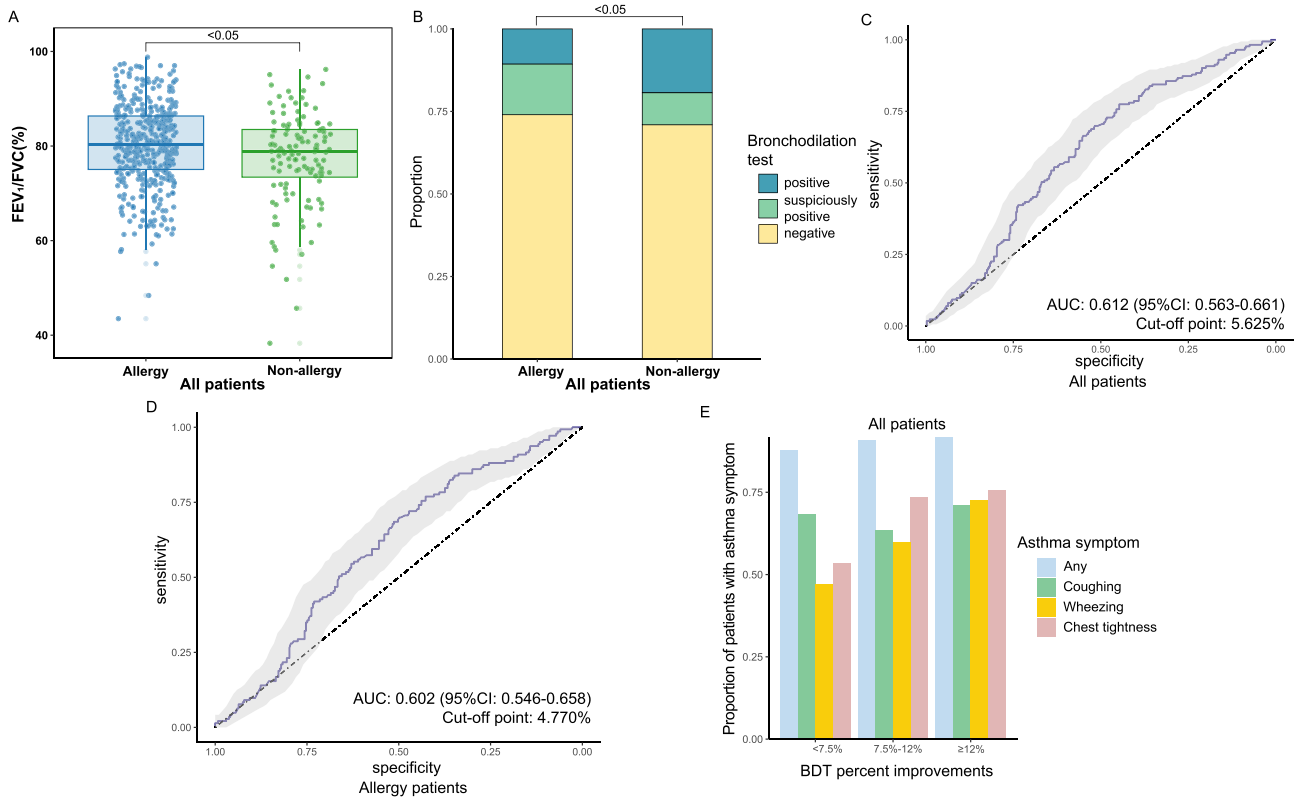

Figure 4 Cut-off value of FEV_1 improvement in bronchodilation test for defining positive criteria in allergic and non-allergic patients. (**A**) Comparison of baseline FEV_1/FVC between allergic and non-allergic patients. (**B**) Proportions of BDT results (positive, suspiciously positive, negative) between allergic and non-allergic patients. (**C** and **D**) ROC curves evaluating the ability of FEV_1 improvement to reflect chest tightness and wheezing in all patients and allergic subgroup. (**E**) Proportions of asthma-related symptoms among patients categorized by FEV_1 improvement <7.5%, 7.5%-12%, or ≥12%.

Abbreviations: AUC, area under the curve; BDT, bronchodilation test; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; ROC, receiver operating characteristic.

FEV_1/FVC (P=0.01) as well a lower BDT positive rate (10.7% vs. 19.4%, P=0.01) than non-allergic patients (Figures 3A, 4A and B). Additionally, allergic patients had higher ratio of BDT suspiciously positive results than non-allergic patients (15.3% vs. 9.7%, P=0.11). Because of the non-specificity of coughing, we excluded it from the suspected asthma symptoms in the following analyses. The ROC curves revealed predictive value of FEV_1% improvements after BDT for symptoms of chest tightness and wheezing in all patients (P<0.001), allergic patients (P=0.001), and non-allergic patients (P=0.02), and with cut-off value of only 5.6% in all patients and even lower (4.8%) in allergic patients (Figure 4C and D, S5). These lower thresholds aligned more closely with symptom patterns and may better capture early or mild disease-related changes. Furthermore, patients with BDT percent improvements of 7.5%-12% had similar proportions of wheezing (59.7% vs. 72.5%, P=0.11) and chest tightness (73.6% vs. 75.7%, P=0.77) symptoms compared to patients of ≥12%. At the same time, patients in 7.5%-12% group had significantly higher proportions of wheezing (59.7% vs. 46.9%, P=0.046) and chest tightness (73.6% vs. 53.3%, P=0.001) symptoms compared to those in <7.5% (Figure 4E). The traditional cutoff value of BDT percent improvements ≥12% could only achieve sensitivity of 15.8% to identify patients with chest tightness or wheezing, and the sensitivity was even lower to 13.5%) in allergic patients. A cut off value of 7.5% could improve sensitivity to 32.2% in all patients and 30.7% in allergic patients (Table 3).

Distinct Characteristics Between Children and Teenagers/Adults Patients

To examine age-related differences in airway reversibility and small airway function, we compared BDT outcomes and small airway parameters between pediatric and adult patients. The baseline characteristics were listed in Supplementary Table 1. The distribution of BDT results was similar ingeneral between children and teenagers/adults, with more children having BDT percent improvements of 7.5%-12% (14.8% vs. 13.6%, P=0.75) (Figure 5A). In addition, the proportion of small

Table 3 Sensitivity and Specificity for Different BDT Positive Cut-off Values to Predict Asthma Symptom (Chest Tightness and Wheezing)

BDT Percent Improvements	All Patients		Allergy Patients		Non-Allergy Patients	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
≥7.5%	0.322	0.844	0.307	0.846	0.366	0.833
≥9%	0.261	0.873	0.247	0.881	0.301	0.833
≥12%	0.158	0.931	0.135	0.937	0.226	0.900

Abbreviation: BDT, bronchodilation test.

airway dysfunction was similar between the children and teenagers/adults (P=0.64) (Figure 5B). By subgroup analyses, we noticed that non-allergic patients in children showed especially high BDT positive rate (33.3%) (Figure 5C); however, this subgroup was small and the findings should be interpreted with caution.

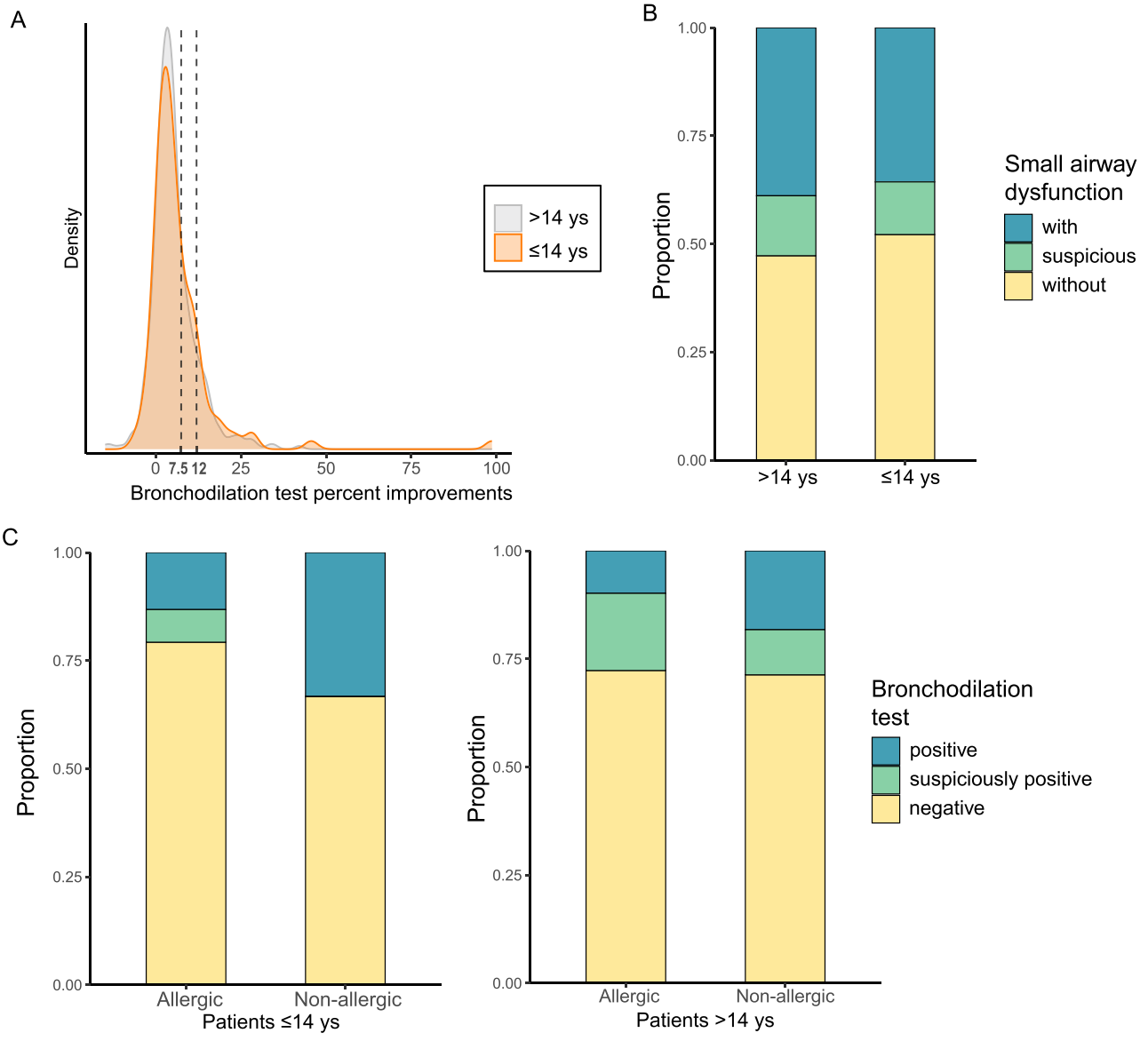

Figure 5 Age-related patterns of bronchodilator responsiveness and small airway dysfunction. (**A**) Density distribution curves of FEV_1 improvements in BDT among patients aged ≤14 years and >14 years. (**B**) Proportions of small airway reversibility among patients aged ≤14 years and >14 years. (**C**) Proportions of BDT results (positive, suspiciously positive, negative) in allergic and non-allergic subgroups among patients aged ≤14 years and >14 years.
Abbreviations: BDT, bronchodilation test; FEV_1, forced expiratory volume in one second.

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Discussion

In this study, we investigated spirometry and BDT results in a real-world Chinese cohort predominantly composed of patients with rhinitis with and without atopy. We examined the distribution of BDR across baseline lung function and its relationship with respiratory symptoms and physiological measures in routine clinical practice. FEV_1/FVC and FEF_{25-75} showed stronger associations with suspected asthma symptoms, particularly chest tightness and wheezing, whereas cough alone was less informative. Both eosinophil counts and proportions were negatively correlated with multiple spirometry indices, especially among non-allergic patients, suggesting distinct inflammatory–functional patterns across phenotypes. Notably, a substantial proportion of patients with preserved baseline lung function (FEV1 ≥80% predicted) still exhibited significant BDR, indicating that reliance on baseline obstruction alone may not fully capture reversible airflow limitations in clinical setting. The conventional ≥ 12% FEV_1 improvement threshold identified only 15.8% of patients with typical asthma symptoms and an even lower proportion (13.5%) of allergic individuals—suggesting that its sensitivity may be lower in this real-world population.

Reconsidering When to Perform BDT

Limiting BDT to only patients with baseline airflow obstruction may lead to underdiagnosis of reversible airway disease.[24] In our cohort, 47.2% of patients with positive BDT had FEV_1≥ 80% predicted, indicating that nearly half of reversible cases would not have been identified if BDT were restricted to patients with overt airflow obstruction. Dufetelle et al also observed significant reversibility in asthmatic children with normal baseline spirometry.[21] BPT is generally safe under standardized protocols and is recommended when diagnostic uncertainty persists. However, our findings suggest that in a subset of patients with rhinitis and asthma-like symptoms and preserved lung function, BDT alone may already provide sufficient physiological evidence of reversible airflow limitation, making immediate bronchial provocation testing unnecessary. Emerging mechanistic studies indicate that bronchoconstriction itself may injure the airway epithelium via crowding-induced cell extrusion; however, direct human evidence remains emerging rather than conclusive.[25] These data support the use of a cautious, stepwise diagnostic strategy. Within this framework, BDT can reasonably be considered a non-provocative first-line physiological assessment, with BPT reserved for cases in which BDT results remain non-diagnostic.

Interpreting Bronchodilator Response Beyond the Conventional Threshold

The conventional threshold of ≥ 12% and ≥ 200 mL FEV_1 improvement remains the most widely applied criterion for defining BDR, yet its empirical basis is limited.[9,20] Several studies have suggested this threshold may be overly stringent, resulting in low sensitivity.[19,26] In our study, this criterion identified only 15.8% of patients with typical asthma-related symptoms and an even lower proportion (13.5%) of allergic individuals. These observations highlight the discrepancy between the established thresholds and spectrum of airflow variability encountered in real-world clinical practice.

Several studies have explored the use of lower thresholds to improve sensitivity. Dundas et al proposed a 9% cutoff with 50% sensitivity in wheezy children.[27] A Chinese cohort suggested a ≥ 7.5% threshold had greater clinical utility.[26] Galant et al revealed that a ≥ 10% FEV_1 improvement was associated with poor asthma control, supporting its prognostic relevance.[28] Consistent with these reports, patients with FEV_1 improvements between 7.5% and 12% in our cohort exhibited symptom profiles similar to those meeting the conventional ≥12% criterion, and distinct from those with <7.5% improvement.

FEV_1 improvements below the conventional ≥12% threshold may therefore provide supportive physiological information in symptomatic patients, although their clinical relevance should be interpreted cautiously. Lowering the threshold inevitably increases sensitivity at the expense of specificity, and small changes of this magnitude may also occur in non-asthmatic individuals, overlapping with physiological variability.[37,38] Accordingly, bronchodilator response should be interpreted in conjunction with the clinical context and follow-up rather than as a stand-alone diagnostic marker. These findings should be considered exploratory and hypothesis-generating, and are not intended to define alternative diagnostic thresholds.

Role of Small Airway Parameters

Small airways parameters, such as FEF_{25-75}, FEF_{50}, and FEF_{75}, provide additional insight into airway dysfunction beyond FEV_1. Previous studies have reported correlations between FEF_{25-75} and BDR in asthmatic children with normal FEV_1,[29] and impaired FEF_{25-75} values have been shown to predict BDR in adults.[39] In our study, FEV_1 could discriminate between patients with and without suspected asthma symptoms; however, indices reflecting small airway function demonstrated stronger associations with symptoms and BDR.

Notably, only 27.3% of patients with suspected asthma symptoms had positive or suspiciously positive BDR, while 53.6% showed evidence of small airway dysfunction. Moreover, most patients with positive BDR also exhibit small airway dysfunction, suggesting that small airway involvement may represent an early or predominant physiological feature in this population. These findings are consistent with the concept that small-airway dysfunction reflects an early phase of asthma pathophysiology.[40,41]

Oscillometry-based techniques, such as impulse oscillometry (IOS), have been shown to provide a sensitive and effort-independent assessment of small airway function and may detect abnormalities not captured by spirometry. Previous studies have demonstrated that oscillometric indices, including R5–R20 and X5, are associated with asthma control, exacerbation risk, and small airway involvement.[42] However, these techniques are not routinely available in many clinical settings. Therefore, spirometry-derived indices, despite their variability, remain widely used in real-world practice and may still provide useful physiological information when interpreted in context.

Rao et al also proposed increase in $FEF_{25-75} \geq 30\%$ to be used as a criterion for BDR, identifying substantially more responders than the conventional FEV_1-based criterion.[30] However, in our cohort, only 15.1% of patients with suspected asthma symptoms met this criterion. This discrepancy may reflect the high variability and volume dependence of FEF-based indices. Because isovolume correction was not available in our system, changes in FEF_{25-75} may have been influenced by concurrent changes in FVC. Therefore, the small airway indices in this study were interpreted as complementary and exploratory measures rather than as standalone diagnostic criteria.

Differences Between Allergic and Non-Allergic Phenotypes

Allergic rhinitis, nonallergic rhinitis, and asthma represent distinct phenotypes with different inflammatory and functional characteristics. Non-allergic asthma is associated with a later disease onset and more severe airflow obstruction.[13] In our cohort, allergic patients had significantly higher FEV_1/FVC ratios and lower rates of positive BDT than non-allergic patients. These findings suggest that airflow reversibility and obstruction may manifest differently across phenotypes, with allergic patients more likely to present with preserved baseline spirometry.

Interestingly, inverse correlations between FEV_1 and eosinophil counts, T-IgE, and FeNO were stronger in non-allergic patients, which is in accordance with Beeh et al[43] This heterogeneity underscores the importance of interpreting spirometric and inflammatory findings within the context of allergic status rather than applying uniform thresholds across phenotypes.

Clinical Biomarkers and Symptom Relevance

Among the evaluated biomarkers, blood eosinophil count showed the strongest association with impaired lung function and positive BDR, consistent with previous studies linking eosinophilia to asthma severity and disease burden.[44,45] In contrast, total IgE and FeNO showed weaker correlations with spirometric parameters.

Clinically, wheezing and chest tightness were more strongly associated with airflow limitation and BDR than was cough alone. These findings support a symptom-informed approach to lung function testing, in which BDT is prioritized for patients with symptoms most suggestive of reversible airway disease. In this context, BDT may help to identify patients who can be physiologically characterized without an immediate need for BPT.

From a clinical perspective, these findings support a stepwise approach to physiological testing in patients with rhinitis and asthma-like symptoms. In patients with suggestive symptoms but preserved baseline spirometry, bronchodilator testing may serve as an initial, non-provocative assessment to identify reversible airflow limitation. For patients with inconclusive results, further evaluation with bronchial provocation testing or longitudinal follow-up may be considered. In this context, spirometric indices, particularly those reflecting small airway function, together with symptom profiles, may help guide the selection and interpretation of diagnostic tests in routine clinical practice.

Limitations

This study has several limitations. First, sensitivity and specificity were estimated within a real-world cohort without a uniform, independent reference diagnosis of asthma. Accordingly, diagnostic performance should be interpreted cautiously. Second, the absence of a dedicated non-asthmatic control group limits the precise estimation of specificity. The comparator group was small and not fully characterized, and therefore cannot be considered a true control population, which may limit the interpretation of specificity and between-group comparisons. Third, information on recent infections, comorbidities, and baseline medication use or withdrawal prior to spirometry was not consistently available in this retrospective dataset, which may have influenced spirometry and bronchodilator responsiveness. In addition, standardized asthma control scores such as the Asthma Control Questionnaire (ACQ) or Asthma Control Test (ACT) were not consistently recorded, limiting the ability to relate BDR to validated measures of symptom control. Fourth, although recent recommendations have proposed using z-scores and alternative definitions of BDR,[34] we adopted widely used criteria to facilitate a comparison with the existing literature. Finally, small-airway indices are inherently variable and volume-dependent, and our findings regarding these parameters should be viewed as exploratory. Prospective studies incorporating standardized diagnostic pathways and well-characterized control populations are required to validate these observations.

Conclusion

In this real-world cohort of patients with rhinitis and asthma-like symptoms, bronchodilator responsiveness was frequently observed, despite preserved baseline spirometry. These findings suggest that airflow variability may be present without overt obstruction and can be identified through bronchodilation testing when interpreted alongside symptoms and spirometric context. Small airway parameters and modest FEV_1 improvements appear to reflect the clinically relevant physiological variability in symptomatic patients. These findings describe patterns of spirometry and bronchodilator responsiveness in patients with rhinitis and asthma-like symptoms, and may inform the interpretation of lung function testing in routine clinical practice.

Abbreviations

AR, allergic rhinitis; BDR, bronchodilator responsiveness; BDT, bronchodilation test; BMI, body mass index; BPT, bronchial provocation test; FeNO, fraction of exhaled nitric oxide; GINA, Global Initiative for Asthma; ROC, receiver operating characteristic.

Ethics Approval

This study was approved by the Ethical Committee of the Peking Union Medical College Hospital (No. I-23PJ573).

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Disclosure

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