

## **A Study on the Necessity of Bronchodilator Testing in Pediatric Patients with Normal Forced Expiratory Volume in One Second, Forced Vital Capacity, and FEV1/FVC Ratio but Small Airway Dysfunction: A Postprint**

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### **Abstract**

**Background:** In clinical practice, children with asthma-related symptoms such as wheezing, cough, and chest tightness initially undergo pulmonary ventilation function testing. When the forced expiratory volume in one second (FEV1) is <70%, it indicates significant airflow limitation or airway obstruction, and a bronchodilator test should be performed. However, some children have normal FEV1 but decreased small airway function, suggesting possible mild airflow limitation or airway obstruction. Furthermore, bronchial provocation testing is relatively complex, expensive, carries certain risks, and many primary-level hospitals lack the equipment and personnel to conduct it. Nevertheless, bronchodilator tests can also be positive in these children, which holds significance for asthma diagnosis.

**Objective:** To investigate the necessity of performing bronchodilator tests in children with normal FEV1, forced vital capacity (FVC), and FEV1/FVC ratio but decreased small airway function.

**Methods:** A case-control study was conducted involving 180 asthmatic children aged 5–14 years with symptoms of wheezing, cough, and chest tightness who presented to the outpatient clinic of the Third Affiliated Hospital of Zhengzhou University from May 29, 2019, to September 20, 2024. All subjects had undergone routine pulmonary ventilation function testing and bronchodilator tests, with results showing normal FEV1, FVC, and FEV1/FVC but decreased small airway function. Using an FEV1 improvement rate of  $\geq 12\%$  as the criterion for a positive bronchodilator test, participants were divided into a positive group (n=33) and a negative group (n=147). Baseline characteristics and pulmonary

ventilation function parameters were compared between the two groups. Pearson correlation analysis was used to examine the correlation between small airway function indices and bronchodilator test results. Receiver operating characteristic (ROC) curve analysis was employed to evaluate the efficacy of small airway function indices for predicting positive bronchodilator test results.

**Results:** Children in the positive bronchodilator test group had significantly lower forced expiratory flow at 50% of forced vital capacity percentage predicted (FEF50%pred), forced expiratory flow at 75% of forced vital capacity percentage predicted (FEF75%pred), and maximal mid-expiratory flow percentage predicted (MMEF%pred) compared with the negative group ( $P < 0.05$ ). FEF50%pred, FEF75%pred, and MMEF%pred all showed correlation with bronchodilator test results ( $P < 0.001$ ). The area under the curve (AUC) values for FEF50%pred, FEF75%pred, and MMEF%pred for predicting positive bronchodilator test results were 0.733 (95% CI=0.644–0.822), 0.827 (95% CI=0.756–0.898), and 0.849 (95% CI=0.789–0.909), respectively, with optimal cutoff values of 66.85%, 50.00%, and 63.35%. The AUC values for combined predictions were 0.859 for FEF50%pred+FEF75%pred, 0.855 for FEF50%pred+MMEF%pred, 0.865 for FEF75%pred+MMEF%pred, and 0.865 for all three indices combined. The AUC of the three-index combination was greater than that of FEF50%pred or FEF75%pred alone ( $Z = -2.801$ ,  $P = 0.005$ ;  $Z = -1.994$ ,  $P = 0.046$ ).

**Conclusion:** For children with asthma-related symptoms such as wheezing, chest tightness, and cough, even when FEV1, FVC, and FEV1/FVC are normal, close attention should still be paid to small airway function indices. When FEF50%pred  $\geq$  66.85%, 50.00%  $\leq$  63.35%, positive bronchodilator test results can be predicted with some degree of accuracy, and bronchodilator tests should be actively performed to assist in asthma diagnosis.

## Full Text

### Preamble

#### To Explore the Necessity of Bronchodilation Test in Children with Normal FEV1, FVC and FEV1/FVC but Decreased Small Airway Function

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### Abstract

**Background:** In clinical practice, children presenting with asthma-related symptoms such as wheezing, cough, and chest tightness should first undergo pulmonary ventilation function examination. When forced expiratory volume

in one second (FEV1) <70%, indicating obvious airflow limitation or airway obstruction, a bronchodilation test should be performed. However, some children have normal FEV1 but decreased small airway function, suggesting possible mild airflow limitation or airway obstruction. While bronchial provocation tests are complex, expensive, carry certain risks, and require equipment and personnel unavailable in many primary hospitals, bronchodilation tests in these children can still yield positive results, which holds significance for asthma diagnosis.

**Objective:** To investigate the necessity of bronchodilation testing in children with normal FEV1, forced vital capacity (FVC), and FEV1/FVC but decreased small airway function.

**Methods:** A case-control study was conducted on 180 children with asthma aged 5–14 years who presented with wheezing, cough, chest tightness, and other symptoms at the outpatient clinic of The Third Affiliated Hospital of Zhengzhou University from May 29, 2019, to September 20, 2024. All subjects underwent routine pulmonary ventilation function examination and bronchodilation test, with results showing normal FEV1, FVC, and FEV1/FVC but decreased small airway function. Using an FEV1 improvement rate  $\geq 12\%$  as the criterion for a positive bronchodilation test, subjects were divided into a positive group (n=33) and a negative group (n=147). Basic data and pulmonary ventilation function indexes were compared between groups. Pearson correlation analysis was used to examine the relationship between small airway function indexes and bronchodilation test results. Receiver operating characteristic (ROC) curves were employed to analyze the predictive efficacy of small airway function indexes for positive bronchodilation test results.

**Results:** The positive group showed significantly lower forced expiratory flow at 50% of vital capacity as percentage of predicted value (FEF50%pred), forced expiratory flow at 75% of vital capacity as percentage of predicted value (FEF75%pred), and maximum mid-expiratory flow as percentage of predicted value (MMEF%pred) compared to the negative group ( $P < 0.05$ ). FEF50%pred, FEF75%pred, and MMEF%pred all correlated with bronchodilation test results ( $P < 0.001$ ). The area under the curve (AUC) for predicting positive bronchodilation test results was 0.733 (95%CI=0.644–0.822), 0.827 (95%CI=0.756–0.898), and 0.849 (95%CI=0.789–0.909) for FEF50%pred, FEF75%pred, and MMEF%pred, respectively, with optimal cutoff values of 66.85%, 50.00%, and 63.35%. The AUCs for combined predictions were 0.859 for FEF50%pred+FEF75%pred, 0.855 for FEF50%pred+MMEF%pred, 0.865 for FEF75%pred+MMEF%pred, and 0.865 for all three indexes combined. The AUC for the three-index combination was greater than that of FEF50%pred or FEF75%pred alone ( $Z = -2.801, -1.994; P = 0.005, 0.046$ ).

**Conclusion:** For children with asthma-related symptoms such as wheezing, chest tightness, and cough, small airway function indexes warrant attention even when FEV1, FVC, and FEV1/FVC are normal. When FEF50%pred  $\geq 66.85\%$ , FEF75%pred  $\geq 50.00\%$ , or MMEF%pred  $\geq 63.35\%$ , positive bronchodilation test results can be predicted to some extent, and bronchodilation testing should

be actively performed to assist in asthma diagnosis.

**[Key words]** Asthma; Bronchial asthma; Child; Bronchodilation test; Decreased small airway function; Forced expiratory volume in one second; Forced vital capacity; Forced expiratory volume in 1 s to forced vital capacity ratio

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## Introduction

Bronchial asthma is a common chronic respiratory disease in children, clinically characterized by recurrent episodes of wheezing, chest tightness, and cough, with pathophysiological features including chronic airway inflammation, airway hyperresponsiveness, and reversible airflow limitation. The incidence of childhood asthma continues to rise in recent years [1-2]. Early diagnosis, early intervention, and standardized treatment play crucial roles in controlling asthma, improving quality of life, and enhancing prognosis. Bronchodilation tests and bronchial provocation tests are commonly used to assist in diagnosing bronchial asthma, differential diagnosis, and treatment adjustment. The former primarily evaluates the reversibility of airflow obstruction, offers high safety and operability, and has been widely applied in clinical practice [3-4]. The latter mainly assesses airway hyperresponsiveness but is more complex, expensive, carries certain risks, and requires equipment and personnel unavailable in many primary hospitals [5-6].

In clinical practice, children with asthma-related symptoms such as wheezing, cough, and chest tightness first undergo pulmonary ventilation function examination. When forced expiratory volume in one second (FEV1) <70%, indicating obvious airflow limitation or airway obstruction, a bronchodilation test should be performed. However, some children have normal FEV1 but decreased small airway function, suggesting possible mild airflow limitation or airway obstruction, and bronchodilation tests can still be positive in these cases, holding significance for asthma diagnosis [7]. Therefore, this retrospective study investigated the necessity of bronchodilation testing in asthmatic children with normal FEV1, forced vital capacity (FVC), and FEV1/FVC but decreased small airway function, and calculated cutoff values for small airway function indexes that predict positive bronchodilation test results. This study can help clinicians, especially those in primary hospitals, determine whether bronchodilation testing is needed when FEV1, FVC, and FEV1/FVC are normal, thereby avoiding missed diagnoses and improving early asthma detection rates.

## Methods

### 1.1 Study Subjects

From May 29, 2019, to September 20, 2024, we selected 180 asthmatic children aged 5–14 years who presented with wheezing, cough, chest tightness, and other symptoms at the outpatient clinic of The Third Affiliated Hospital of Zhengzhou University and underwent pulmonary ventilation function examination and bronchodilation testing.

**Inclusion criteria:** (1) Age 5–14 years; (2) Clinical diagnosis of asthma [8]; (3) Routine pulmonary ventilation function examination showing normal FEV<sub>1</sub>, FVC, and FEV<sub>1</sub>/FVC but decreased small airway function [FEV<sub>1</sub> percentage of predicted value (FEV<sub>1</sub>%pred)  $\geq$  80%, FVC percentage of predicted value (FVC%pred)  $\geq$  80%, FEV<sub>1</sub>/FVC percentage of predicted value (FEV<sub>1</sub>/FVC%pred)  $\geq$  92%, but forced expiratory flow at 50% of vital capacity (FEF<sub>50</sub>) and/or forced expiratory flow at 75% of vital capacity (FEF<sub>75</sub>) and/or maximum mid-expiratory flow (MMEF) percentage of predicted value (MMEF%pred)  $\geq$  65%] [9].

**Exclusion criteria:** (1) Diseases other than asthma affecting pulmonary ventilation function; severe heart, liver, kidney, or other organ dysfunction; (2) Inability to cooperate with pulmonary function examination, contraindications for routine pulmonary ventilation function or bronchodilation testing, or treatment with corticosteroids within 4 weeks before the visit. This study was approved by the Ethics Committee of The Third Affiliated Hospital of Zhengzhou University (Approval No. 2024-205-01). As a retrospective study, informed consent was waived.

### 1.2 Methods

**1.2.1 General Data** General data including age, sex, height, and weight were collected from the hospital's electronic medical record system.

**1.2.2 Pulmonary Ventilation Function Examination** According to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines [10], trained professionals performed routine pulmonary ventilation function testing using a MasterScreen IOS spirometer (Germany). Each child completed at least three tests meeting quality control standards, with the best result selected for analysis. Pulmonary ventilation function indexes included: FVC%pred, FEV<sub>1</sub> percentage of predicted value (FEV<sub>1</sub>%pred), FEV<sub>1</sub>/FVC%pred, MMEF%pred, forced expiratory flow at 25% of vital capacity percentage of predicted value (FEF<sub>25</sub>%pred), FEF<sub>50</sub> percentage of predicted value (FEF<sub>50</sub>%pred), and FEF<sub>75</sub> percentage of predicted value (FEF<sub>75</sub>%pred). Predicted values for pulmonary ventilation function parameters were calculated using the Zapletal prediction equation.

**1.2.3 Bronchodilation Test and Grouping** Before bronchodilation testing, children discontinued medications that could affect results. Terbutaline sulfate nebulization solution (Hebei Renhe Yikang Pharmaceutical Co., Ltd.) was administered via inhalation at a dose of 2.5 mg (for body weight  $\leq 20$  kg) or 5 mg (for body weight  $>20$  kg), with pulmonary ventilation function measured after 15 minutes of nebulization. The improvement rate for pulmonary ventilation parameters was calculated as: (post-medication value - pre-medication value)/pre-medication value  $\times 100\%$ . A bronchodilation test was considered positive when FEV1 improvement rate  $\geq 12\%$  [7]. Based on test results, children were divided into two groups: positive group (33 cases) and negative group (147 cases).

### 1.3 Statistical Analysis

Data were analyzed using SPSS 26.0 software. Categorical data were expressed as number of cases and percentage (%) and compared between groups using the  $\chi^2$  test. Normally distributed continuous data were expressed as mean  $\pm$  standard deviation ( $\bar{x} \pm s$ ) and compared using independent samples t-test. Non-normally distributed continuous data were expressed as median (P25, P75) and compared using Mann-Whitney U test. Pearson correlation analysis was used to examine the relationship between small airway function indexes and bronchodilation test results. Receiver operating characteristic (ROC) curves were used to evaluate the predictive value of small airway function indexes for positive bronchodilation test results. Area under the curve (AUC)  $<0.7$  indicated low predictive efficacy, 0.7–0.9 indicated moderate efficacy, and  $>0.9$  indicated high efficacy [11]. Comparisons between AUCs were performed using Delong's test.  $P < 0.05$  was considered statistically significant.

## Results

### 2.1 Comparison of Basic Data and Pulmonary Function Indexes Between Two Groups

This study included 180 children, comprising 114 males (63.33%) and 66 females (36.67%), with a median age of 7.0 (6.0, 9.0) years. No significant differences were found between groups in sex, BMI, FEV1%pred, FVC%pred, or FEF25%pred ( $P > 0.05$ ). However, the positive bronchodilation test group showed significantly lower age, FEV1/FVC%pred, FEF50%pred, FEF75%pred, and MMEF%pred compared to the negative group ( $P < 0.05$ ).

### 2.2 Correlation Between Small Airway Function Indexes and Bronchodilation Test Results

Pearson correlation analysis of small airway function indexes FEF50%pred, FEF75%pred, and MMEF%pred with bronchodilation test results showed significant correlations: FEF50%pred ( $r=0.308$ ), FEF75%pred ( $r=0.459$ ), and MMEF%pred ( $r=0.453$ ) (all  $P < 0.001$ ) [Figure 1: see original paper].

### 2.3 Predictive Efficacy Analysis of Small Airway Function Indexes for Positive Bronchodilation Test Results

ROC curve analysis revealed that the AUCs for predicting positive bronchodilation test results were 0.733 (95%CI=0.644–0.822), 0.827 (95%CI=0.756–0.898), and 0.849 (95%CI=0.789–0.909) for FEF50%pred, FEF75%pred, and MMEF%pred, respectively, with optimal cutoff values of 66.85%, 50.00%, and 63.35%. Using binary logistic regression models, pairwise and three-way combinations of these single indexes were fitted, returning predicted probabilities as independent test variables. ROC curves were plotted, yielding AUCs of 0.859, 0.855, 0.865, and 0.865 for FEF50%pred+FEF75%pred, FEF50%pred+MMEF%pred, FEF75%pred+MMEF%pred, and all three indexes combined, respectively. The three-index combination showed high sensitivity (90.9%) and specificity (70.1%). The AUC for the three-index combination was significantly greater than that of FEF50%pred or FEF75%pred alone ( $Z=-2.801, -1.994$ ;  $P=0.005, 0.046$ ). However, no significant differences were found when comparing the three-index combination with MMEF%pred alone or with two-index combinations ( $Z=-0.934, -0.768, -1.038, -0.199$ ;  $P=0.350, 0.442, 0.299, 0.842$ ) [Figure 2: see original paper].

## Discussion

This study explored the necessity of bronchodilation testing in children with normal FEV1, FVC, and FEV1/FVC but decreased small airway function, and determined optimal cutoff values for small airway function indexes to predict positive bronchodilation test results. The findings demonstrate that FEF50%pred, FEF75%pred, and MMEF%pred have predictive value for positive bronchodilation test results, with optimal predictive efficacy achieved when all three indexes are combined.

Our results showed that while FEV1, FVC, and FEV1/FVC did not differ significantly between the positive and negative bronchodilation test groups ( $P>0.05$ ), FEF50%pred, FEF75%pred, and MMEF%pred were significantly lower in the positive group ( $P<0.001$ ) and correlated with bronchodilation test results, suggesting that decreased small airway function may be an early marker of airflow limitation in asthmatic children. Chronic inflammation in asthmatic children often involves the entire airway, particularly small airways [12]. Small airways are defined as those below the terminal bronchioles with diameter  $<2$  mm, numerous in quantity, large in total cross-sectional area, relatively rich in smooth muscle, lacking cartilage support, prone to closure, and susceptible to early disease involvement—changes that large airway function indexes such as FEV1 and FVC cannot sensitively reflect [13-14].

Previous studies have shown that small airway dysfunction can exist in early-stage asthma before abnormalities appear in large airway function indexes like FEV1 [15]. A study of 1,631 asthmatic children with normal large airway function indexes found that 217 had small airway dysfunction, with a bronchodila-

tion test positive rate of 28.57% [16]. Shi et al. [17] reported that the degree of decline in small airway function indexes positively correlated with positive bronchodilation test results. Our findings further support these views, suggesting that in children with normal FEV1, FVC, and FEV1/FVC, decreased small airway indexes may indicate occult airflow limitation, providing a physiological basis for positive bronchodilation test results. Therefore, clinical practice should emphasize monitoring of small airway function indexes, and bronchodilation testing should be actively performed to assist in asthma diagnosis even when large airway function indexes are normal, thereby reducing missed diagnosis rates.

This study determined optimal cutoff values for FEF50%pred, FEF75%pred, and MMEF%pred to predict positive bronchodilation test results as 66.85%, 50.00%, and 63.35%, respectively. MMEF%pred showed an AUC of 0.849, likely related to its reflection of mid-expiratory flow characteristics, as airflow during this phase primarily depends on small airway function [9]. Studies have found that MMEF can change early in asthmatic children [18], indicating its sensitivity to airway obstruction. Another study found that MMEF had stronger diagnostic efficacy for asthma than other routine single pulmonary function indexes and could more effectively differentiate asthmatic from non-asthmatic children [19]. Furthermore, research has shown that MMEF independently correlates with asthma severity [20], consistent with our findings. Additionally, Zhan et al. [21] reported that cutoff values of 70.690% for FEF50%pred and 66.665% for MMEF%pred could effectively differentiate asthmatic from non-asthmatic children. A study of adult asthma showed that cutoff values of 67.95%, 59.75%, and 69.25% for FEF50%pred, FEF75%pred, and MMEF%pred, respectively, could effectively distinguish between positive and negative bronchodilation test groups [22]. Our cutoff values are similar to those reported in these studies, though specific cutoff values for predicting positive bronchodilation test results in children have not been previously established. Moreover, the combined AUC of all three indexes (0.865) was greater than that of FEF50%pred or FEF75%pred alone ( $P < 0.05$ ), with high sensitivity (90.9%) and specificity (70.1%), indicating that combined use of these indexes improves predictive comprehensiveness and avoids limitations of single indexes, providing more reliable evidence for clinical decision-making. Therefore, this study provides a theoretical basis for determining when to perform bronchodilation testing in children with asthma-related symptoms and normal FEV1, FVC, and FEV1/FVC but decreased small airway function indexes.

In summary, for children with asthma-related symptoms such as wheezing, chest tightness, and cough, small airway function indexes warrant attention even when FEV1, FVC, and FEV1/FVC are normal. When FEF50%pred  $\geq$  66.85%, FEF75%pred  $\geq$  50.00%, or MMEF%pred  $\geq$  63.35%, positive bronchodilation test results can be predicted to some extent, and bronchodilation testing should be actively performed to assist in asthma diagnosis.

This study focused on early changes in small airway function and innovatively

proposed multiple small airway function indexes as predictors of positive bronchodilation test results, calculating cutoff values to help clinicians determine the need for bronchodilation testing when FEV1 and FVC are normal, thereby avoiding missed diagnoses and improving early asthma detection rates. This is particularly meaningful in primary hospitals where the high cost and complexity of bronchial provocation tests limit their clinical application, while this study provides an alternative approach based on small airway function indexes. However, this study has limitations. First, as a single-center study with a relatively small sample size, the results may have limited generalizability. Future multi-center collaborative studies with larger sample sizes are needed. Additionally, as a retrospective study, prospective studies are needed to further validate the accuracy of these small airway function indexes in predicting positive bronchodilation test results and explore their applicability across different age groups and disease stages.

**Author Contributions:** XIONG Xiaoman was responsible for data collection, analysis, and interpretation, and drafting the manuscript. LI Aijun and ZHENG Yuehong were responsible for data collection. ZHANG Yanli and YANG Qiuyan provided critical review and guidance on the intellectual content of the article.

**Conflict of Interest:** None declared.

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