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ORIGINAL RESEARCH

Application of Impulse Oscillometry Combined with Fractional Exhaled Nitric Oxide in Monitoring Asthma Control Levels in Children

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Video abstract

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Purpose: To investigate whether Impulse Oscillometry (IOS) could more effectively monitor children with uncontrolled asthma and evaluate small airway function changes, while establishing a prediction model in combination with fractional exhaled nitric oxide (FeNO) to assist in clinical management and treatment of asthmatic children.

Patients and Methods: A retrospective study was conducted on 203 asthmatic children who were followed up in our hospital from August 2023 to August 2024. Patients were divided into controlled asthma group (n=80) and uncontrolled asthma group (n=123). Conventional ventilatory parameters, IOS parameters, FeNO levels, and clinical data were analyzed and compared between the two groups. The optimal prediction model was established through multivariate logistic regression.

Results: In the uncontrolled asthma group, the respiratory system impedance at 5 hz (Z5), resistance at 5 hz (R5), the difference between resistance at 5 hz and resistance at 20 hz (R5-R20), resonant frequency (Fres), and FeNO levels were significantly higher compared to the controlled asthma group. The ratio of forced expiratory volume in one second to forced vital capacity (FEV_1/FVC), forced expiratory flow at 50% (FEF50), forced expiratory flow at 75% (FEF75), and maximal mid-expiratory flow (MMEF) were lower in the uncontrolled group ($P<0.05$). Receiver operating characteristic curve (ROC) analysis demonstrated that Z5, R5, R5-R20, Fres, and FeNO were valuable in asthma diagnosis ($P<0.05$), with higher sensitivity in monitoring small airway function compared to MMEF. Multivariate logistic regression analysis established the optimal prediction model combining R5+(R5-R20) +FeNO, with an area under curve (AUC) of 0.915 ($P<0.05$), sensitivity of 0.831, and specificity of 0. 892.

Conclusion: Compared to conventional pulmonary function tests, IOS effectively identifies uncontrolled status in asthmatic children, particularly in younger patients, with higher sensitivity to small airway function changes. The model comprising R5+(R5-R20) +FeNO demonstrates clinical value in identifying uncontrolled status in asthmatic children.

Keywords: impulse oscillometry, conventional pulmonary function, fractional exhaled nitric oxide, asthma control, children

Introduction

Bronchial asthma is one of the most common chronic diseases in children, with approximately 7–10% of children globally suffering from asthma.[1] The typical characteristics of asthma include airway inflammation, airway hyperresponsiveness, and reversible airflow limitation.[2] Effective asthma control can reduce the frequency of asthma symptoms, lower the risk of acute exacerbations, and improve the quality of life of children with asthma.[3] Research has shown that lung function in children with asthma does not always fully correlate with their clinical symptoms. Some children with milder symptoms may still have significant airway obstruction, while children with well-controlled symptoms may have increased airway reactivity due to hidden small airway inflammation.[4,5] Therefore, asthma control strategies relying on

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subjective symptom assessment may have certain limitations, while objective lung function monitoring can provide more reliable feedback on the disease status.[6]

Common lung function tests, such as pulmonary ventilation function tests and bronchodilator tests, include measurements of forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1), can reflect the degree of airway obstruction.[7] For children with well-controlled asthma, FEV_1 values are typically above 80% of the predicted value.[8] However, traditional lung function tests require patients to take deep breaths and forcefully exhale, which may be challenging for young children (especially those under 6 years old) or patients with severe conditions to complete.[9] Therefore, it is particularly important to find non-invasive lung function assessment methods that are suitable for young children and patients who are unable to cooperate with complex examinations.

Impulse oscillometry (IOS), a non-invasive lung function test that does not require forced exhalation, has been increasingly applied in the management of childhood asthma in recent years.[10] Unlike traditional lung function tests, IOS measures airway resistance and reactivity by applying low-frequency oscillatory waves while the patient breathes calmly. It has become a more practical method, particularly for young children who cannot accurately perform forced exhalation.[11] IOS can measure the function of both large and small airways, and it is especially sensitive to small airway lesions, which is crucial in the early stages of asthma and in children with mild symptoms.[12]

Fractional exhaled nitric oxide (FeNO) levels are an important indicator reflecting airway inflammation, particularly airway responses mediated by Th2 cells, and are especially associated with eosinophilic inflammation.[13] A systematic review has investigated the application of FeNO in the management of childhood asthma, indicating that FeNO can effectively predict treatment response in children with asthma and help identify disease changes early.[14]

This study compares various parameters of conventional pulmonary ventilation, IOS, and FeNO examinations between children with controlled asthma and those with uncontrolled asthma. It explores whether IOS can more effectively monitor children with inadequate asthma control, especially those cases with small airway lesions that have not been revealed in conventional lung function tests. Additionally, predictive models are developed to enhance identification capabilities, providing assistance for further strengthening the clinical management and treatment of children with asthma during outpatient follow-up.

Materials and Methods

Study Subjects

We retrospectively collected data on children with asthma who visited the outpatient clinic or were hospitalized in the Department of Pediatric Respiratory Medicine at Chengdu Women's and Children's Central Hospital from August 2023 to August 2024. The inclusion criteria were as follows: 1. Children with a definite diagnosis of asthma; 2. Children who received standardized asthma treatment and follow-up at the Department of Pediatric Respiratory Medicine in our hospital from August 2023 to August 2024; 3. Children who completed IOS, pulmonary ventilation function, and FeNO examinations. The exclusion criteria were as follows: 1. Children with other respiratory diseases, congenital heart disease, immunodeficiency diseases, or other underlying diseases; 2. Children with unqualified IOS, pulmonary ventilation function, or FeNO examinations. The diagnosis of asthma was based on the criteria from the "Guidelines for the Diagnosis and Prevention of Childhood Bronchial Asthma (2016 Edition)".[15]

Study Contents

All children with asthma underwent pulmonary function tests, IOS, and FeNO measurements on the same day during follow-up. We retrospectively collected data on the children, including age, gender, weight, height, body mass Index (BMI), pulmonary function test parameters, IOS parameters, and FeNO parameters. The participating children with asthma were assessed for asthma control using age-appropriate clinical a ssessment tools such as the Asthma Control Test (ACT), Childhood Asthma Control Test (C-ACT), and Test for Respiratory and Asthma Control in Kids (TRACK),[16] based on the scoring results, children with ACT scores ≤19, C-ACT scores ≤19, or TRACK scores<80 are classified into the uncontrolled asthma group, while those with the opposite scores are classified into the controlled asthma group.[16]

Instrumentation and Measurement Methods

Impulse Oscillometry

Impulse oscillometry (IOS) was performed using the Master Screen IOS device (Jaeger, Germany) according to the recommendations of the American Thoracic Society/European Respiratory Society (ATS/ERS) on forced oscillation techniques.[17] During the examination, the children breathed calmly and avoided shallow, rapid, or deep breathing. Care was taken to avoid mouthpiece obstruction/leakage, glottic closure, and swallowing movements. The operator gently pressed the subject's cheeks with both hands to avoid cheek vibrations from affecting the accuracy of the measurement. The breathing curve on the volume-time graph was smooth, and the measurement was repeated 3–5 times, with each measurement lasting no less than 30 seconds.[18] To ensure the accuracy of the detection, the coherence (Co) value at 5 hz should be >0.8 cm H_2O, and the Co value at 20 hz should be between 0.9–1.0 cm H_2O. The measured IOS parameters included: respiratory system impedance at 5 hz (Z5) (measured/predicted value), resistance of the respiratory system at 5 hz (R5) (measured/predicted value), resistance of the respiratory system at 20 hz (R20) (measured/predicted value), the difference between resistance at 5 hz and at 20 hz (R5-R20), the difference in reactance of the respiratory system at 5 hz (ΔX5, measured X5 - predicted X5), and resonant frequency (Fres). Among these, R5 reflected the total airway resistance, while R20 reflected the central airway resistance. In contrast, R5-R20, X5, and Fres reflected the degree of peripheral airway obstruction. Currently, most domestic studies use foreign prediction equations, and the normal values for the main parameters are as follows: R5 < 120% of the predicted value; R20 < 120% of the predicted value; X5 > predicted value - 0.2 kPa/(L·s); Fres < predicted value + 10 Hz.[19]

Pulmonary Ventilation Function Testing

Pulmonary ventilation function testing was conducted using the Jaeger pulmonary function test system (Germany), following ATS/ERS recommendations.[17] In a calm state, the child was positioned upright with a nose clip applied to pinch both nostrils, the teeth were used to bite down on the mouthpiece, the lips formed a tight seal to prevent air leakage, and the tongue did not block the mouthpiece. The flow-volume loop measurement was then performed.[7] The best measurement values from three acceptable and repeatable forced expiratory maneuvers were recorded, including forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), forced expiratory flow at 50% of FVC (FEF50), forced expiratory flow at 75% of FVC (FEF75), maximal mid-expiratory flow (MMEF), and the FEV_1/FVC ratio. An FVC or FEV_1 measured value/expected value of <80% was considered abnormal, an FEV_1/FVC measured value/expected value of <92% was considered abnormal, and FEF50, FEF75, and MMEF measured values/expected values of <65% were considered abnormal.[7]

Fractional Exhaled Nitric Oxide Measurement

Fractional exhaled nitric oxide (FeNO) was measured with a nitric oxide analyzer (Guangzhou Repro Medical Technology Co., Ltd.), following the ATS/ERS guidelines.[17] The results were expressed in parts per billion (ppb). The subjects inhaled ambient air through a nitric oxide filter to their total lung capacity and then exhaled at a constant flow rate of 50 mL/s (±5%) for 10 seconds to clear the airway cavity and reach a plateau phase. Children under 12 years old needed to exhale for at least 4 seconds, while children over 12 years old and adults needed to exhale for at least 6 seconds. The NO level was measured during the last 3 seconds of the plateau phase. Currently, both domestically and internationally, the recommended clinical interpretation of FeNO levels from the 2011 guidelines established by the American Thoracic Society is still used, with values >20 ppb considered abnormal.[20]

Statistical Analysis

Statistical analysis was performed using IBM SPSS 27.0 software and GraphPad Prism 6 software.[21] The Kolmogorov–Smirnov test was used to determine whether the data followed a normal distribution. The Mann–Whitney *U*-test was used to compare differences in IOS, pulmonary ventilation function, and FeNO between subjects in the asthma-controlled group and the asthma-uncontrolled group. Univariate logistic regression analysis was employed to evaluate the association between abnormal IOS parameters or FeNO values and uncontrolled asthma status, the strength of the association between variables was measured using regression coefficients (B values) and 95% confidence intervals (CI), with statistical significance assessed by P-values. Receiver operating characteristic (ROC) curve analysis was performed to assess the discriminatory ability of IOS parameters, FeNO, and the combination of IOS parameters and FeNO. The DeLong test was used to compare the areas under the ROC curves (AUC), AUC >0.7 was of clinical diagnostic value.[22] Multivariate logistic regression analysis and stepwise regression analysis were applied to construct predictive models. A P-value <0.05 was considered statistically significant.

Results

General Information

The study included a total of 203 children with asthma, of which 80 were in the asthma-controlled group and 123 were in the asthma-uncontrolled group. The mean age of the asthma-controlled group was 6.35 ± 2.14 years, with 42.5% of the children being female. The mean age of the asthma-uncontrolled group was 5.94 ± 2.14 years, with 43.9% of the children being female. No significant differences were observed between the controlled and uncontrolled asthma groups regarding age, gender, height, weight or BMI (P > 0.05), as shown in Table 1.

Comparison of Pulmonary Ventilation, IOS Parameters, and FeNO Between the Asthma-Controlled Group and the Asthma-Uncontrolled Group

In the pulmonary ventilation test, there were no statistically significant differences in the FVC and FEV_1 between the asthma-controlled group and the asthma-uncontrolled group (P > 0.05). However, the FEV_1/FVC parameter was higher in the asthma-controlled group compared to the asthma-uncontrolled group (P< 0.001). Additionally, the small airway function indicators such as FEF50, FEF75, and MMEF were lower in the asthma-uncontrolled group compared to the asthma-controlled group (P < 0.001). In the IOS assessment, parameters such as Z5, R5, Fres, and R5-R20 were all significantly higher in the asthma-uncontrolled group compared to the asthma-controlled group (P < 0.001), whereas ΔX5 and R20 showed no significant differences (P > 0.05). The FeNO value was also higher in the asthma-uncontrolled group than in the asthma-controlled group (P =0.047), as shown in Table 2.

ROC Curve Analysis of Pulmonary Ventilation, IOS Parameters, and FeNO in Predicting Uncontrolled Asthma

ROC curve analysis indicated that the FEV_1/FVC ventilation function index and the small airway function index MMEF are valuable for identifying asthma control status in children (P < 0.001). Additionally, IOS parameters (Z5, R5, R5-R20, Fres) and FeNO assessment were also effective in distinguishing asthma control status in children (P < 0.001), as shown in Table 3.

Table 1 Demographic Characteristics of the Study Population

	Asthma-Controlled Group	Asthma-Uncontrolled Group	P-value
Sample Size	80	123	
Age (years)	6.35 (2.14)	5.94 (2.14)	0.12
Female (%)	42.5%	43.9%	0.84
Weight (kg)	25.55 (12.71)	22.22 (7.81)	0.20
Height (cm)	121.8 (16.61)	118.8 (14.60)	0.21
BMI (kg/m²)	16.85(7.17)	15.60(3.44)	0.75

Notes: Values are presented as mean (SD) unless otherwise specified.
Abbreviation: BMI, body mass Index.

Table 2 Comparison of Pulmonary Ventilation, IOS, and FeNO Parameters Between Asthma-Controlled and Uncontrolled Groups

Variable	Asthma-Controlled Group (n=80)	Asthma-Uncontrolled Group (n=123)	P-value
Pulmonary-Ventilation Parameters			
FVC (%)	98.88 (14.71)	95.88 (16.41)	0.956
FEV_1(%)	102.7 (13.61)	97.77(19.27)	0.258
FEV_1/FVC (%)	101.0 (7.61)	96.19 (9.85)	**<0.001**
FEF50 (%)	87.30 (24.49)	70.46 (23.37)	**<0.001**
FEF75 (%)	83.28 (4.37)	75.90 (14.32)	**<0.001**
MMEF (%)	87.20 (29.07)	69.06 (24.81)	**<0.001**
IOS Parameters			
Z5 (%)	96.02 (21.05)	127.7 (26.91)	**<0.001**
R5 (%)	98.15 (18.70)	128.8 (26.76)	**<0.001**
R20 (%)	93.06 (15.39)	98.35(23.66)	0.13
ΔX5 ($cmH_20/L/s$)	−0.73 (0.69)	−0.99 (1.16)	0.15
Fres (Hz)	18.31 (3.75)	22.85 (3.80)	**< 0.001**
R5-R20 (%)	21.74 (7.78)	32.10(9.62)	**< 0.001**
FeNO (ppb)	17.30 (2.26)	26.03 (3.00)	**0.047**

Notes: The bolded P-values in the tables indicate statistical significance.
Abbreviations: FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; FEF50, forced expiratory flow at 50% of FVC; FEF75, forced expiratory flow at 75% of FVC; MMEF, maximal mid-expiratory flow; Z5, respiratory system impedance at 5 hz; R5, resistance of the respiratory system at 5 hz; R20, resistance of the respiratory system at 20 hz; ΔX5, the difference in reactance of the respiratory system at 5 hz; Fres, resonant frequency; R5-R20, the difference between resistance at 5 hz and at 20 hz; FeNO, fractional exhaled nitric oxide.

Table 3 ROC Curve Analysis of Pulmonary Ventilation, IOS Parameters, and FeNO

Variable	AUC	95% CI	Optimal Cutoff Value	Sensitivity	Specificity	Youden Index	P-value
FVC	0.502	0.421~0.584	99.2%	0.4463	0.4125	0.1412	0.96
FEV_1	0.551	0.465~0.638	86.45%	0.1927	0.9848	0.1775	0.26
FEV_1/FVC	0.651	0.569~0.734	93.65%	0.3670	0.8788	0.2458	**0.001**
MMEF	0.685	0.609~0.760	78.45%	0.7131	0.6500	0.3631	**< 0.001**
Z5	0.836	0.781~0.892	110.5%	0.7561	0.7750	0.5311	**< 0.001**
R5	0.835	0.780~0.891	112.6%	0.7398	0.8250	0.5648	**< 0.001**
R20	0.563	0.484~0.642	96.6%	0.5082	0.6750	0.1832	0.13
ΔX5	0.575	0.474~0.676	−0.390	0.7711	0.3922	0.1633	0.15
Fres	0.827	0.769~0.885	20.25Hz	0.8455	0.7250	0.5705	**< 0.001**

(*Continued*)

Table 3 (Continued).

Variable	AUC	95% CI	Optimal Cutoff Value	Sensitivity	Specificity	Youden Index	P-value
R5-R20	0.794	0.734~0.854	34.02%	0.4390	0.9875	0.4265	**< 0.001**
FeNO	0.621	0.507~0.735	20.5ppb	0.4576	0.8378	0.2954	**0.047**

Notes: The bolded P-values in the tables indicate statistical significance.
Abbreviations: AUC, area under the curve; 95% CI, 95% confidence intervals; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; MMEF, maximal mid-expiratory flow; Z5, respiratory system impedance at 5 hz; R5, resistance of the respiratory system at 5 hz; R20, resistance of the respiratory system at 20 hz; ΔX5, the difference in reactance of the respiratory system at 5 hz; Fres, resonant frequency; R5-R20, the difference between resistance at 5 hz and at 20 hz; FeNO, fractional exhaled nitric oxide.

Comparison of AUC Values Between IOS and Pulmonary Ventilation-Related Parameters

Using the DeLong test, the AUC values of total airway resistance parameters in IOS, such as Z5 and R5, were found to be more predictive than those of lung ventilation parameters FVC, FEV_1, and FEV_1/FVC ($P < 0.001$). Similarly, small airway function-related parameters Fres and R5-R20 in IOS were found to have greater predictive value than MMEF in the pulmonary ventilation test, showing statistical significance (P =0.007 and P=0.025) as shown in Table 4 and Figure 1A and B).

Univariate Logistic Regression Analysis of IOS Parameters and FeNO for Identifying Uncontrolled Asthma

The results of the univariate logistic analysis showed that in uncontrolled asthma, the IOS parameters Z5, R5, Fres, and R5-R20 were significantly associated with uncontrolled asthma status ($P < 0.001$), with odds ratios (OR) of 1.068, 1.068, 1.448, and 1.147, respectively. The 95% CI were 1.068~1.048, 1.048~1.088, 1.287~1.630, and 1.098~1.197, respectively. Additionally, FeNO was also significantly associated with identifying uncontrolled asthma status (P=0.049), with an OR of 1.028 and a 95% CI of 1.000~1.058, as shown in Table 5.

Table 4 Area Differences Under the ROC Curve for IOS and Pulmonary Ventilation Parameters

Variable	Z-value	AUC Difference	Standard Error	95% CI	P-value
Z5 - FVC	5.816	0.336	0.274	0.223~0.449	**< 0.001**
Z5 - FEV_1	5.118	0.285	0.271	0.176~0.394	**< 0.001**
Z5 - FEV_1/FVC	3.703	0.189	0.267	0.089~0.289	**< 0.001**
R5 - FVC	5.873	0.336	0.273	0.224~0.448	**< 0.001**
R5 - FEV_1	5.184	0.284	0.271	0.177~0.392	**< 0.001**
R5 - FEV_1/FVC	3.707	0.189	0.266	0.089~0.288	**< 0.001**
Fres - MMEF	2.712	0.135	0.262	0.038~0.233	**0.007**
(R5-R20) - MMEF	2.246	0.101	0.262	0.013~0.190	**0.025**

Notes: The bolded P-values in the tables indicate statistical significance.
Abbreviations: AUC, area under the curve; 95% CI, 95% confidence intervals; Z5, respiratory system impedance at 5 hz; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; MMEF, maximal mid-expiratory flow; R5, resistance of the respiratory system at 5 hz; Fres, resonant frequency; R5-R20, the difference between resistance at 5 hz and at 20 hz.

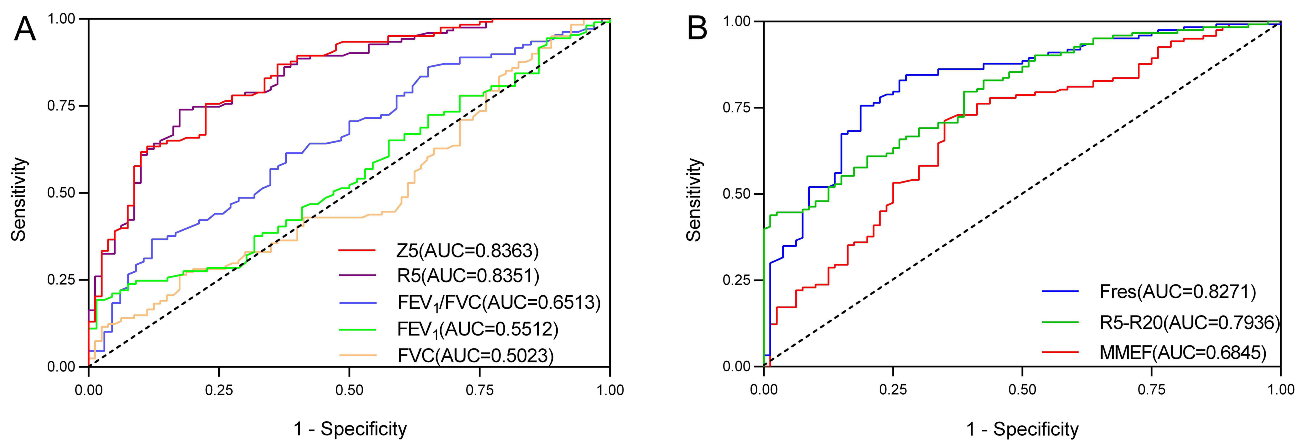

Figure 1 ROC Curve Analysis of IOS and Pulmonary Ventilation Parameters, (**A**) ROC curves for Z5, R5, FEV_1, FVC, FEV_1/FVC. (**B**) ROC curves for Fres, R5-R20, MMEF.
Abbreviations: Z5, respiratory system impedance at 5 hz; R5, resistance of the respiratory system at 5 hz; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; Fres, resonant frequency; R5-R20, the difference between resistance at 5 hz and at 20 hz; MMEF, maximal mid-expiratory flow.

Analysis of Differences in Identifying Uncontrolled Asthma Between IOS Alone and Combined FeNO

The results indicated that combining FeNO with individual IOS parameters (Z5, R5, Fres, R5-R20) did not significantly increase the AUC values compared to IOS alone ($P > 0.05$). Therefore, combining FeNO with each parameter individually did not markedly enhance the ability to identify asthma control status in children, as shown in Table 6 and Figure 2.

Multivariate Logistic Regression Analysis and Model Recommendation for Predicting Uncontrolled Asthma in Children Using IOS and FeNO-Related Parameters

Based on univariate logistic regression analysis, the parameters Z5, R5, R5-R20, and FeNO were statistically significant. These parameters were then included in a multivariate logistic regression analysis, with variable selection performed by stepwise regression. The results showed that the optimal predictive model was determined to be R5 + (R5-R20) + FeNO, with the regression equation: Logit (P) = −0.594 + 0.006*R5 + 0.014*(R5-R20) + 0.005*FeNO. ROC curve analysis showed an AUC for this model of 0.915 ($P < 0.001$), with a sensitivity of 0.831 and specificity of

Table 5 Univariate Logistic Regression Analysis of IOS Parameters and FeNO

Variable	B	Standard Error	Wald	OR	95% CI	P-value
Z5%	0.066	0.010	45.577	1.068	1.068~1.048	**<0.001**
R5%	0.065	0.010	45.479	1.068	1.048~1.088	**<0.001**
R20%	0.013	0.008	3.043	1.013	0.998~1.029	0.08
ΔX5 (cmH20/L/s)	0.340	0.246	1.914	1.405	0.868~2.273	0.17
Fres (Hz)	0.370	0.060	37.864	1.448	1.287~1.630	**<0.001**
R5-R20%	0.137	0.022	38.432	1.147	1.098~1.197	**< 0.001**
FeNO (ppb)	0.028	0.014	3.882	1.028	1.000~1.058	**0.049**

Notes: B denotes regression coefficient. The bolded P-values in the tables indicate statistical significance.
Abbreviations: OR, Odds Ratio; 95% CI, 95% confidence intervals; Z5, respiratory system impedance at 5 hz; R5, resistance of the respiratory system at 5 hz; R20, resistance of the respiratory system at 20 hz; ΔX5, the difference in reactance of the respiratory system at 5 hz; Fres, resonant frequency; R5-R20, the difference between resistance at 5 hz and at 20 hz; FeNO, fractional exhaled nitric oxide.

Table 6 Comparison of AUC for IOS and Pulmonary Ventilation Parameters Combined with FeNO in Identifying Uncontrolled Asthma

Variable	AUC	Variable +FeNO	AUC	95% CI	P-value
Z5	0.836	Z5+FeNO	0.846	−0.081~0.011	0.14
R5	0.835	R5+FeNO	0.850	−0.078~0.012	0.15
Fres	0.827	Fres +FeNO	0.869	−0.022~0.075	0.29
R5-R20	0.794	(R5-R20) +FeNO	0.799	−0.022~0.070	0.31

Abbreviations: 95% CI, 95% confidence intervals; AUC, area under the curve; Z5, respiratory system impedance at 5 hz; R5, resistance of the respiratory system at 5 hz; Fres, resonant frequency; R5-R20, the difference between resistance at 5 hz and at 20 hz.

0.892 (as shown in Table 7 and Figure 3). The DeLong test indicated that this predictive model was superior to individual parameters Z5, R5, R5-R20, and FeNO ($P < 0.05$) (as shown in Table 8), suggesting a high value for predicting uncontrolled asthma in children.

Discussion

In recent years, the incidence of asthma among children has been steadily increasing.[1] Effective asthma control not only improves patients' quality of life but also reduces the risk of acute exacerbations and healthcare costs.[2] Therefore, assessing asthma control status during long-term outpatient follow-up is crucial. Pulmonary function testing plays a key role in evaluating asthma control in children. It not only allows for an objective assessment of airway patency and monitoring of respiratory function changes but also aids in risk identification, evaluation of therapeutic efficacy, and promotion of education and self-management for pediatric patients and their families.[23] However, with the increasing demands for the diagnosis and treatment of respiratory diseases, the limitations of conventional pulmonary function tests have become increasingly apparent. Specifically, traditional methods struggle to meet clinical needs in assessing small

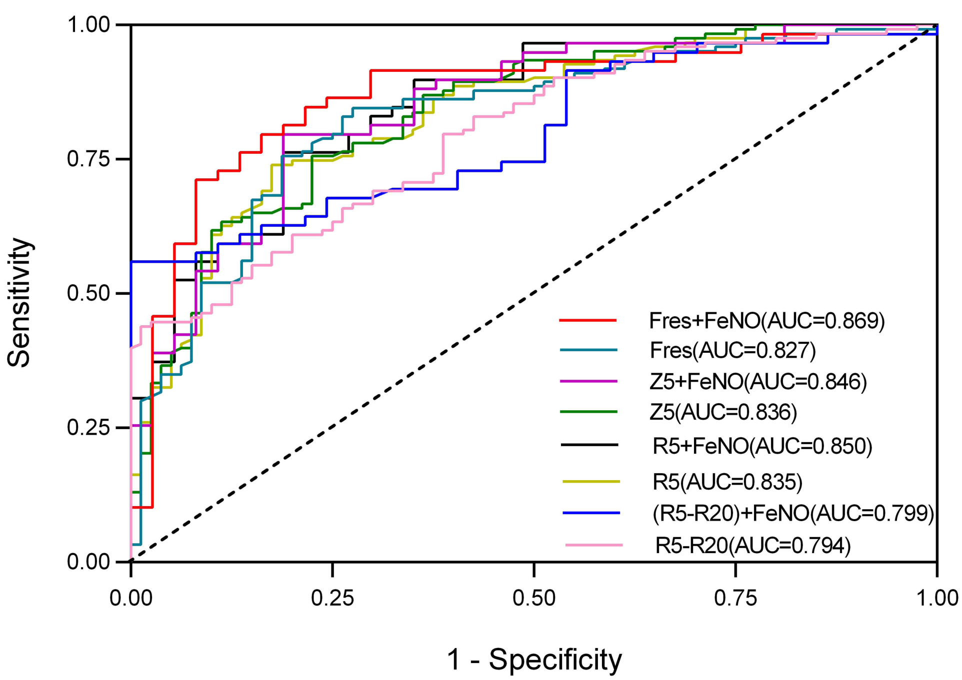

Figure 2 ROC Curve Analysis of IOS Parameters Combined with FeNO.
Abbreviations: Z5, respiratory system impedance at 5 hz; R5, resistance of the respiratory system at 5 hz; R5-R20, the difference between resistance at 5 hz and at 20 hz; Fres, resonant frequency; FeNO, fractional exhaled nitric oxide.

Table 7 Multivariate Logistic Regression Analysis for Predicting Uncontrolled Asthma

Variable	B	Standard Error	Wald	OR	95% CI	P-value
Z5%	−0.171	0.106	2.578	0.843	0.684~1.038	0.11
R5%	0.231	0.107	4.697	1.260	1.022~1.553	**0.030**
Fres (Hz)	0.132	0.111	1.410	1.141	0.918~1.418	0.24
R5-R20%	0.145	0.047	9.368	1.156	1.053~1.268	**0.002**
FeNO (ppb)	0.053	0.020	6.762	1.055	1.013~1.098	**0.009**

Notes: B denotes regression coefficient. The bolded P-values in the tables indicate statistical significance.
Abbreviations: OR, Odds Ratio; 95% CI, 95% confidence intervals; Z5, respiratory system impedance at 5 hz; R5, resistance of the respiratory system at 5 hz; Fres, resonant frequency; R5-R20, the difference between resistance at 5 hz and at 20 hz; FeNO, fractional exhaled nitric oxide; ppb, parts per billion.

airway function and conducting pulmonary function tests in children.[24] The emergence and development of IOS provide new approaches and solutions to address these challenges.[24]

The findings of this study reveal that there were no significant differences in pulmonary ventilation parameters such as FVC and FEV_1 between the asthma-controlled and uncontrolled groups. However, IOS indicators such as Z5, R5, R5-R20, and Fres were significantly higher in the uncontrolled group than in the controlled group, this suggests that IOS is more sensitive in identifying uncontrolled asthma states, even when pulmonary ventilation of large airways is normal. Moreover, although there is no difference in FVC and FEV_1, the FEV_1/FVC ratio in the uncontrolled asthma group showed difference, which may be related to small airway dysfunction and exacerbated airway inflammation and remodeling caused by poor asthma control.[25,26] The small airway function indicators FEF50, FEF75, and MMEF were higher in the uncontrolled asthma group than in the controlled group. Recent studies have shown that small airways in asthma patients are more susceptible to airway remodeling and inflammation than large airways, especially in poorly

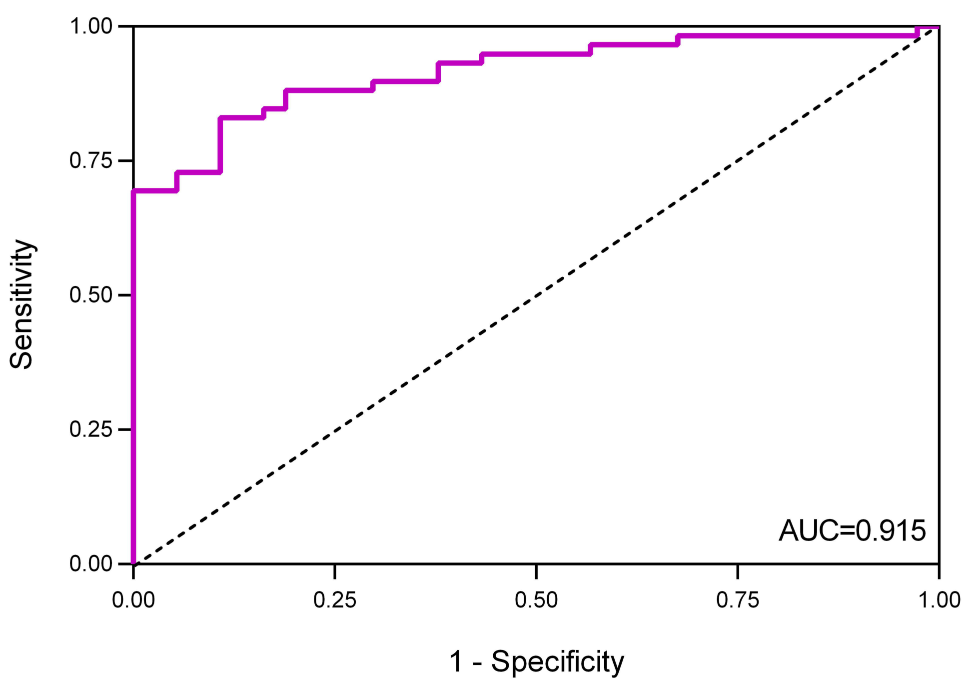

Figure 3 ROC Curve Analysis for the R5 + (R5-R20) + FeNO Model.
Abbreviation: AUC, area under the curve.

Table 8 Comparison of AUC Between Predictive Models and Single Parameters

Variable	Z-value	AUC Difference	Standard Error	95% CI	P-value
Model - Z5	2.647	0.104	0.269	0.027~0.181	**0.008**
Model - R5	2.521	0.099	0.267	0.022~0.176	**0.012**
Model - (R5-R20)	3.354	0.140	0.272	0.058~0.222	**0.001**
Model - FeNO	4.898	0.294	0.293	0.177~0.412	**<0.001**

Notes: Model: R5 + (R5-R20) + FeNO. The bolded P-values in the tables indicate statistical significance.
Abbreviations: AUC, area under the curve; 95% CI, 95% confidence intervals; Z5, respiratory system impedance at 5 hz; R5, resistance of the respiratory system at 5 hz; R5-R20, the difference between resistance at 5 hz and at 20 hz; FeNO, fractional exhaled nitric oxide.

controlled conditions.[27] Pathological changes in small airways usually precede large airway dysfunction, so they are essential for the long-term control assessment of asthma.[28] Evidence also indicates that MMEF can effectively differentiate asthma control levels, especially when FEV_1 remains within normal limits. Changes in MMEF can reflect early functional damage to small airways.[29,30] IOS can measure small airway resistance such as Fres and R5-R20 at low airflow rates, detecting changes that traditional pulmonary function tests cannot reveal. For those asthma patients who appear asymptomatic, changes in their small airway function can provide important clues for evaluating asthma control.[31] Combined with the ROC curve analysis results of this study, MMEF has a high recognition value for determining asthma control, and IOS-related parameters (such as Z5, R5, R5-R20, Fres) and FeNO can also effectively distinguish between controlled and uncontrolled asthma states. Through DeLong test analysis, we found that IOS parameters for small airway function assessment, including Fres and R5-R20, demonstrated superior predictive value compared to MMEF. This suggests that IOS exhibits high sensitivity and specificity in predicting uncontrolled asthma status, particularly in small airway function monitoring. Similar conclusions were reached in studies by Zeng, Jing et al.[32]

Based on our findings, traditional pulmonary ventilation tests such as FVC and $FEV_{1,}$ often require high levels of patient cooperation, which are difficult to achieve in younger children. For pediatric patients who are unable to complete traditional pulmonary function tests, IOS provides an effective alternative.[11] Through simple breathing maneuvers requiring minimal cooperation, IOS sensitively detects subtle airway changes, making it particularly suitable for children aged 3 to 6 years.[22] However, despite its advantages in monitoring asthma in younger children, the standalone use of IOS to predict asthma control has limitations. While IOS reflects airway resistance changes, it is less sensitive to airway inflammation, such as eosinophilic inflammation.[22] Therefore, a single IOS indicator may overlook important factors such as airway inflammation. FeNO detection is mainly used to assess the inflammatory state of the airways.[13] For asthma patients with eosinophilic inflammation, FENO levels are often closely related to asthma control levels.[33] The combination of IOS and FeNO enables asthma evaluation from two dimensions: airway function and inflammation. The respiratory resistance and reactance data provided by IOS, together with airway inflammation levels reflected by FeNO, not only improve diagnostic accuracy but also provide more reliable evidence for treatment planning.[21] In this study, combined analysis of IOS and FeNO revealed that Z5, R5, R5-R20, and FeNO are independent predictors of uncontrolled asthma. A multivariate regression analysis developed the optimal predictive model: R5 + (R5-R20) + FeNO. This model achieved an AUC of 0.915 ($P < 0.05$), with a sensitivity of 0.831 and a specificity of 0. 892. This AUC exceeds any single IOS parameter, demonstrating the model's enhanced sensitivity and specificity in predicting uncontrolled asthma. The combined prediction model compensates for IOS's limitations in identifying asthma inflammation, providing a more comprehensive evaluation based on both airway impedance and inflammation factors.

Limitations and Strengths

This study highlights the potential of IOS in monitoring asthma control status. Its advantages in complementing conventional pulmonary function tests are particularly evident in the evaluation of small airway function and in young children with asthma. As a non-invasive testing method, IOS offers a novel reference for the long-term clinical management of asthma. However, this study has several limitations. Firstly, it is a single-center study lacking data from other regions, necessitating further research with a larger sample size. Secondly, previous studies have demonstrated that body weight status affects IOS measurements,[34] as obesity influences respiratory system impedance through alterations in chest wall compliance and respiratory muscle function.[35,36] In our study, although the BMI of children in the controlled and uncontrolled asthma groups were 16.85 kg/m² and 15.60 kg/m², respectively, and both fell within the normal weight range (5th-85th percentile), this limits the applicability of our predictive model to asthmatic children with normal BMI only. This suggests that future studies should conduct stratified analyses based on different weight status to enhance the generalizability of the prediction model. Additionally, the widespread adoption of this combined detection strategy faces challenges, such as the need to establish standardized reference values and interpretation protocols. Further research is also needed to clarify the correlation between these two indices and their clinical significance.

Conclusion

In conclusion, IOS could become a central tool for the personalized management and long-term follow-up of pediatric asthma, particularly in younger children. Combined with FeNO, it offers a promising approach for predicting asthma control levels, helping children achieve better long-term control and quality of life. Future multicenter studies are warranted to validate these findings and bring greater benefits to the diagnosis and treatment of respiratory diseases.

Ethics and Consent Statements

The ethics board of Chengdu Women and Children Center Hospital (Ethical number: [2021]203). Written informed consent to participate in this study was provided by the participants' legal guardian. The study complied with the Declaration of Helsinki.

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Disclosure

The authors report no conflicts of interest in this work.

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