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# Impulse Oscillometry Combined to FeNO in Relation to Asthma Control Among Preschool Children

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**Objective:** We aimed to observe and analyze the differences in impulse oscillometry (IOS) and fractional expiratory nitric oxide (FeNO) in relation to asthma control among preschool children, and to explore the predictive value of IOS combined with FeNO for uncontrolled asthma.

**Methods:** This study enrolled 171 preschool children with asthma and 30 healthy preschool children between June 2022 and June 2023. We categorized the asthmatic children as having controlled asthma (n=85) and uncontrolled asthma (n=86) after a 3-month follow-up. IOS and FeNO were collected on the first visit at baseline. Differences in metrics were compared between controlled asthma, uncontrolled asthma and healthy control groups. The area under the receiver operating characteristic curve (AUROC) was utilized to explore the discriminative ability of IOS and FeNO, alone or in combination, against uncontrolled asthma.

**Results:** Compared to the controlled asthma group, the IOS values of R5, X5, R5-R20, and Fres were significantly higher in the uncontrolled asthma group, except for R20. R5 and R5-R20 had the highest area under the curve (AUC), which could reach 0.74 (95% CI 0.66–0.82) and 0.72 (95% CI 0.64–0.80). R20 had the lowest AUC of 0.59. The AUC for FeNO alone was 0.88 (95% CI 0.84–0.93) with a cutoff value of 17.50 ppb, sensitivity and specificity of 0.73 and 0.89. The AUCs of all IOS metrics combined with FeNO were significantly higher, with the highest AUC of 0.92 (95% CI 0.87–0.96) for R5-R20+FeNO, and with a sensitivity and specificity of 0.88 and 0.84.

**Conclusion:** There were significant differences in IOS and FeNO in relation to asthma control among preschooler children. FeNO might be the best predictor of asthma control, and adding any of IOS metrics increased moderately the predictive value.

**Keywords:** asthma control, impulse oscillometry, fractional expiratory nitric oxide, preschool children

## Introduction

Asthma is the most common chronic airway disease in children, which is a heterogeneous disease characterized by chronic airway inflammation and reversible airway obstruction.[1] Asthma in children usually begins early in life, and about 50% of asthmatics have wheezing symptoms by age 6.[2] The impairment of lung function due to persistent asthma typically starts at this stage.[3] Early diagnosis and intervention in childhood asthma are very important. According to the Global Initiative for Asthma (GINA), asthma control is assessed in two domains: symptom control and risk of adverse outcomes, and it is necessary to assess symptom control over the last 4 weeks and identify any other risk factors for exacerbations, persistent airflow limitation or side-effects.[1] Poor symptom control is burdensome to patients and increases the risk of exacerbations, but patients with good symptom control can still have severe exacerbations.[4] Current guidelines recommend using clinical symptoms and spirometry to assess asthma control.[5] However, this is very challenging. Symptoms reported by family members or carers are often not a true reflection of asthma control.[6] Additionally, spirometry may correlate poorly with asthma control symptoms.[7] Previous studies have shown that

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peripheral airway damage is associated with acute asthma exacerbations and the level of asthma control.[8,9] Spirometry had limited value in assessing peripheral airway injury,[10,11] and required the patient to breathe hard, making it difficult for poorly understood and cooperative preschoolers.

It has been suggested that incorporating impulse oscillometry (IOS) alongside spirometry in the guidelines may enhance the identification of uncontrolled asthma, predict future exacerbations, and facilitate targeted therapies.[12] The IOS utilizes externally applied pressure signals and flow rates to generate resistance (Rrs) and reactance (Xrs) between 5 and 20Hz to assess central airway function and peripheral airway function, reflecting the different physiological characteristics of asthma.[13] According to the recommendations of the European Respiratory Society, IOS can be measured starting at 2 years of age.[14] Several studies have shown the predictive value of IOS in identifying preschool children at risk of developing impaired airway function, or asthma, or both. IOS has demonstrated the ability to predict acute asthma exacerbations[15] and assess asthma control.[16,17] Moreover, IOS in preschool children can predict spirometry, active asthma and impaired lung function at school age.[18,19] Fractional exhaled nitric oxide (FeNO) is a quantitative, noninvasive, simple and safe measure of airway inflammation that is strongly associated with eosinophils in children with asthma.[20] FeNO is a good surrogate marker for eosinophilic airway inflammation.[21] Previous studies have shown that elevated FeNO in preschool children is associated with future risk of wheezing or asthma and may predict decreased lung function in infants with recurrent wheezing.[22,23] Patients with both elevated peripheral blood eosinophil counts and FeNO scores had higher rates of asthma exacerbations across all asthma severities.[24] In children with uncontrolled moderate-to-severe asthma, blood eosinophil counts and FeNO were clinically relevant biomarkers to identify those at risk for asthma exacerbations.[25] These two tests offer additional information about airway pathology that spirometry may fail to capture. Currently, there are limited studies on the combination of IOS and FeNO to assess asthma control in preschool children. Most previous work has focused on children aged 6 and above or adults. In previous research, our group constructed a prediction model by combining IOS and FeNO to assess the risk of asthma in preschool children with wheezing, which showed a potential predictive value.[26] After gaining relevant experience, we began to follow up and evaluate the control of asthma in preschool children. This is an extension and supplement to our clinical application research of IOS combined with FeNO.

In this study, we primarily aimed to observe differences in IOS parameters and FeNO in relation to asthma control among preschool children. The objective was to preliminarily investigate the value of combining IOS with FeNO in the assessment of asthma control and to explore cut-points for differentiating uncontrolled asthma. This approach aims to provide a promising tool for asthma management in preschool children.

# Methods

## Study Participants

This prospective study was conducted at a specialized children's hospital in Zhejiang Province, China, from June 2022 to June 2023. The participants included children aged 3–6 years diagnosed with asthma in outpatient clinics and inpatient wards, who underwent follow-up visits. Ethical approval for the study was obtained from the Ethics Committee of the Institutional Review Board of Hangzhou Children's Hospital (2021–14). Informed consent was obtained from all the parents or guardians of minors.

### Inclusion Criteria

1) age 3–6 years old, male or female; 2) diagnosis of bronchial asthma by a specialist according to the diagnostic recommendations of the modified asthma predictive index (mAPI);[27] 3) receiving initial anti-asthma treatment for at least 3 months, with regular daily use of low-dose inhaled corticosteroid (ICS); 4) having succeeded in IOS and FeNO measurements at inclusion; and 5) having completed the 3 months follow-up.

### Exclusion Criteria

1) comorbidity with other chronic respiratory diseases; 2) comorbidity with other systemic chronic diseases; 3) fail to complete the 3 months follow-up; 4) acute exacerbation 4 weeks before study enrollment requiring systemic

corticosteroids; 5) having used ICS, short acting bronchodilators, or both within 6 hours before IOS measurement; 6) having strenuous exercise 4 hours before FeNO test; 7) having high-nitrogen foods or other stimulants 2 hours before FeNO test.

### Grouping Criteria

All enrolled children underwent a medical history inquiry, IOS and FeNO measurements by a specialist at their first visit and required initial anti-asthma treatment with regular daily use of low-dose ICS for at least 3 months. After 3 months of treatment, they were asked to return to the hospital for a second follow-up visit. Their asthma control was assessed by specialists who were blinded to the lung function result, according to the "GINA assessment of asthma control in children 5 years and younger" criteria:[1] in the last 4 weeks, 1) daytime asthma symptoms for more than a few minutes, more than once a week? 2) any activity limitation due to asthma? (runs/plays less than other children, tires easily during walks/playing?) 3) short-acting beta$_2$-agonist reliever (SABA) medication needed more than once a week? 4) any night waking or night coughing due to asthma?

Children without any of these criteria were classified into "controlled group", and those meeting 3–4 of these criteria were classified into "uncontrolled group". In addition, 30 healthy children (same age and sex ratio, no history of asthma or other lung diseases) who presented to the hospital for a health checkup during the same study period were included in the healthy group.

## Impulse Oscillometry

The MasterScreen IOS instrument (Jaeger, Germany) was operated by a professional technician after adequate training following the last technical standards for respiratory oscillometry.[28] Patients were instructed to breathe in a relaxed and stable manner, seated in upright posture with correct head position, cheek support, mouthpiece seal and tongue position. The operator gently pressed both sides of the child's cheeks, avoiding swallowing, coughing, breath-holding, and vocalization. At least three replicates were made, and the minimum acquisition time was at least 30s. Measured values were accepted when the coefficient of variability of at least 3 sets of data were within 15%. The measured IOS indices included resistance at 5 Hz (R5) and 20 Hz (R20), the differences between R5 and R20 (R5-R20), reactance at 5 Hz (X5), and resonant frequency (Fres). In China, the reference normal values for IOS currently used in most hospitals were: R5 less than 120% of the predicted value; R20 less than 120% of the predicted value. X5 greater than the predicted value-0.2 kPa/(L.s); and Fres less than the predicted value +10 Hz.[29]

## FeNO Measurement

The FeNO was measured using a nitric oxide analyzer with electrochemical sensors (Sunvou-CA2122, Jiangsu, China) by a professional technician after adequate training following the ATS/ERS guidelines.[30] Patients were instructed to refrain from eating, drinking, and exercising for 2 hours before FeNO measurements. Online measurement method was used in this study. While seated upright, the child took a breath to empty the lungs, held a disposable bacterial filter in the mouth, and maintained smooth, slow exhalation into the test apparatus for at least 4 seconds to allow the airway compartment to be washed out and a reasonable plateau achieved. The average FeNO value for the 3-second plateau period was recorded. Repeated and reproducible exhalations were performed to obtain at least two FeNO plateau values that agree within 10% of each other. The parameter was expressed in parts per billion (ppb).

## Sample Size

The objective of this study was to assess the predictive efficacy of IOS combined with FeNO on asthma control. The ROC curve module of the PASS software was utilized to determine the sample size. The expected area under the curve (AUC) for the combined model was 0.87.[31] Calculations based on $\alpha$=0.05, $\beta$=0.2, and power=1−$\beta$=80% indicated that a minimum of 66 cases should be included in each group. Accounting for a 20% dropout rate, a minimum of 83 cases should be enrolled in each group.

## Statistical Analysis

Continuous variables were expressed as mean ± SD (standard deviation) or the median and inter-quartile range (25th percentile, 75th percentile), depending on data distribution. The Shapiro–Wilk test was used to check for normality in all variables. Group comparisons were conducted using one-way ANOVA with the Bonferroni correction for normally distributed data and Kruskal–Wallis tests for non-normally distributed data. Count data were expressed as cases (%), and the comparison utilized the chi-square test or Fisher's exact probability method. Receiver operating characteristic (ROC) curves were employed to assess the efficacy of IOS indicators alone and in combination with FeNO in determining uncontrolled asthma. Cutoff values, area under the curve (AUC), sensitivity, and specificity were calculated. All statistical analyses were performed using R version (4.2.2) and graphs prepared using GraphPad Prism 9. A $p$-value of $< 0.05$ was considered statistically significant.

# Results

## Demographic Characteristics of the Study Population

Of the 195 recruited asthmatic children aged 3–6 years, 5 subjects had comorbidities with other chronic respiratory diseases, 6 subjects were unable to cooperate in completing the IOS and FeNO tests, 10 subjects had used systemic corticosteroids, 3 subjects failed to complete the 3 months follow-up, and these subjects were excluded, leaving 171 asthmatic children for the final analysis. In addition, we included 30 healthy control children aged 3–6 years. The included participants had a median age of 49 months, with 114 males and 87 females. Following the specialists' follow-up assessments, 85 asthmatic children were ultimately classified as the controlled asthma group, and 86 asthmatic children as the uncontrolled asthma group. The demographic data of the three groups are presented in Table 1. No significant differences were observed in age, gender, height, and weight, indicating that the three populations were comparable at baseline (all $p > 0.05$). The history of allergic rhinitis was more prevalent in children in the asthma group than in the healthy control group.

## The IOS and FeNO Parameters of the Study Population

The IOS and FeNO parameters of the children in the three groups are shown in Table 2 and Figure 1. In comparison to the controlled asthma group, both the absolute and % predicted values of R5 and X5 parameters were significantly higher in the uncontrolled asthma group. Absolute values of R5-R20 and Fres were statistically different between two groups. Although the absolute and % predicted values of R20 showed a tendency to be higher in the uncontrolled asthma group, the differences were not statistically significant. All IOS indicators were significantly elevated in the uncontrolled asthma group compared to the healthy control group, except for the % predicted value of R20. No statistical differences were observed in R5, X5, R20, R5-R20, and Fres between the controlled asthma group and the healthy control group (all $p > 0.05$). The median FeNO was 6 ppb in the healthy control group, 11 ppb in the controlled asthma group, and 23 ppb in the uncontrolled asthma group. Two-by-two comparisons between groups yielded statistically significant results.

**Table 1** Demographic Characteristics of the Study Population

| Variables | Controlled-Asthma (n=85) | Uncontrolled-Asthma (n=86) | Healthy (n=30) | *p*-value |
|---|---|---|---|---|
| Age, month, M (P25, P75) | 49.00 (44.00, 62.00) | 51.50 (43.00, 58.00) | 47.00 (40.25, 52.75) | 0.176[#] |
| Male, n (%) | 51 (60.00%) | 46 (53.49%) | 17 (56.67%) | 0.691 |
| Height, cm, M (P25, P75) | 105.00 (101.60, 110.60) | 105.50 (102.23, 112.80) | 104.05 (100.78, 111.32) | 0.275[#] |
| Weight, Kg, M (P25, P75) | 18.00 (16.00, 19.00) | 17.25 (16.00, 19.80) | 16.60 (15.65, 19.15) | 0.447[#] |
| Allergic rhinitis history, n (%) | 57 (67.06%) | 47 (54.65%) | 9 (30.00%) | 0.002 |
| Atopic dermatitis history, n (%) | 27 (31.76%) | 40 (46.51%) | 8 (26.67%) | 0.058 |

**Notes**: All data were collected from the children at baseline. Significance level of group difference using Kruskal–Wallis [#]test.

**Table 2** The IOS and FeNO Parameters of the Study Population

| Variables | Controlled-Asthma (n=85) | Uncontrolled-Asthma (n=86) | Healthy-Group (n=30) | Controlled vs Uncontrolled | Controlled vs Healthy | Uncontrolled vs Healthy | *p*-value |
|---|---|---|---|---|---|---|---|
| R5, kPa/(L·s) | 1.17±0.15 | 1.37±0.28 | 1.08±0.14 | <0.001[&] | 0.206[&] | <0.001[&] | <0.001[&] |
| R5, % predicted | 105.30 (96.20, 116.20) | 141.10 (129.48, 155.68) | 103.75 (94.35, 112.40) | <0.001[#] | 1.0[#] | <0.001[#] | <0.001[#] |
| X5, kPa/(L·s) | −0.37 (−0.48, −0.31) | −0.44 (−0.63, −0.34) | −0.37 (−0.54, −0.28) | 0.014[#] | 1.0[#] | 0.041[#] | 0.005[#] |
| X5, % predicted | 102.80 (85.15, 122.80) | 126.10 (96.97, 166.23) | 102.45 (85.58, 119.65) | <0.001[#] | 1.0[#] | 0.002[#] | <0.001[#] |
| R20, kPa/(L·s) | 0.82±0.11 | 0.86±0.13 | 0.79±0.09 | 0.145[&] | 0.576[&] | 0.020[&] | 0.014[&] |
| R20, % predicted | 92.60 (82.30, 101.65) | 95.85 (84.10, 105.10) | 85.95 (80.85, 97.10) | 0.581[#] | 0.466[#] | 0.055[#] | 0.055[#] |
| R5-R20, kPa/(L·s) | 0.35±0.13 | 0.52±0.24 | 0.29±0.16 | <0.001[&] | 0.625[&] | <0.001[&] | <0.001[&] |
| Fres, L/s | 21.38 (19.15, 23.19) | 23.92 (21.97, 27.99) | 21.06 (17.45, 23.58) | <0.001[#] | 1.0[#] | <0.001[#] | <0.001[#] |
| FeNO, ppb | 11.00 (8.00, 14.00) | 23.00 (17.00, 28.00) | 6.00 (4.00, 7.00) | <0.001[#] | <0.001[#] | <0.001[#] | <0.001[#] |

**Notes**: All data were collected from the children at baseline. % predicted, represents the percentage ratio of the actual value to the predicted value. All data were presented as mean ± SD or median (P25, P75) depending on data distribution. Significance level of group difference using Kruskal–Wallis [#]test or one-way ANOVA with the Bonferroni [&]Correction.

**Abbreviations**: R5, resistance at 5 Hz; X5, reactance at 5 Hz; R20, resistance at 20 Hz; Fres, resonant frequency; R5-R20, the differences between R5 and R20.

## The Discriminative Ability of IOS and FeNO for Uncontrolled Asthma

The discriminative ability of IOS/FeNO alone and IOS combined with FeNO between uncontrolled asthma and controlled asthma was illustrated using ROC curves (Table 3 and Figure 2). Among the IOS metrics, R5 had the highest AUC of 0.74 (95% CI 0.66–0.82) at a cut-off value of 1.29 kPa/(L·s), with sensitivity and specificity of 0.62 and 0.86, respectively, followed by R5-R20 at a cut-off value of 0.46 kPa/(L·s), with an AUC of 0.72 (95% CI 0.64–0.80), with

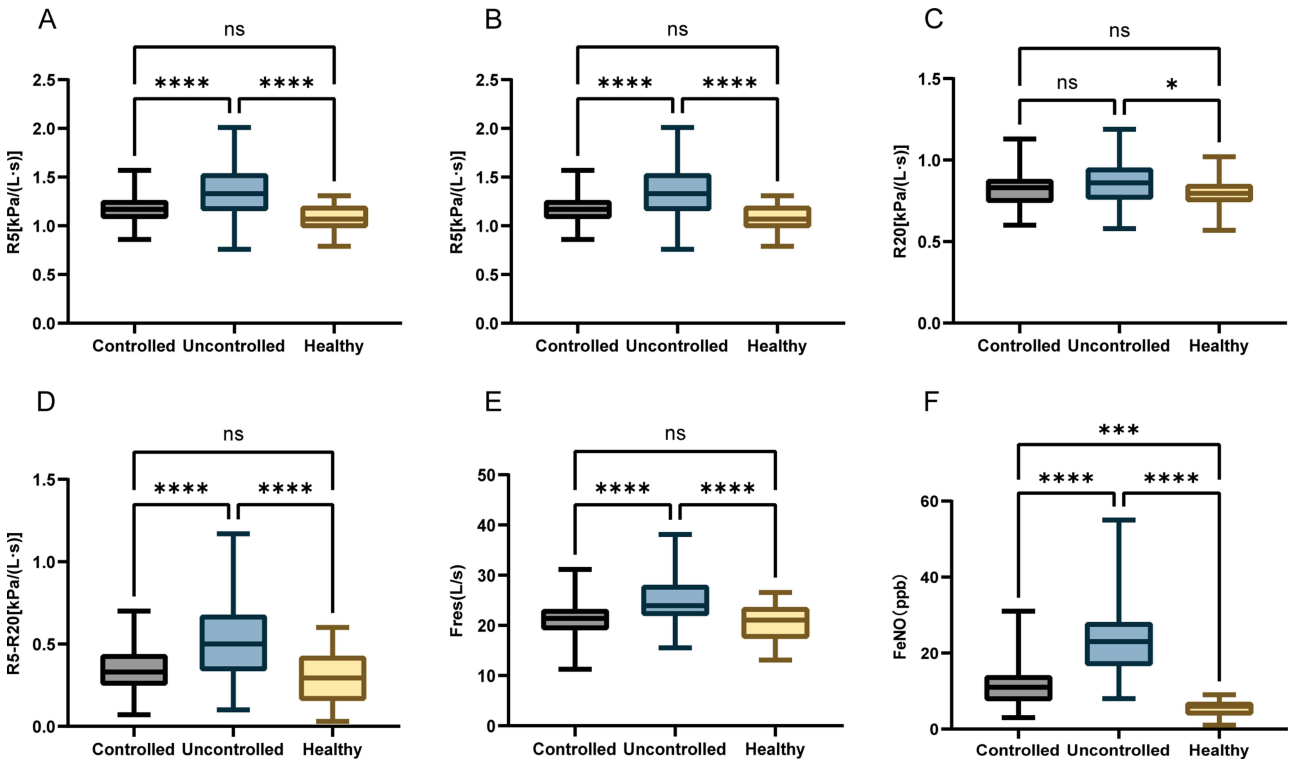


**Figure 1** Box plots of IOS measurements ((**A**) R5, (**B**) X5, (**C**) R20, (**D**) R5-R20, (**E**) Fres) and FeNO (**F**) for different asthma groups and healthy groups. Significance level of group difference using Kruskal–Wallis test or one-way ANOVA with the Bonferroni correction: ns, no statistical difference; *p-value < 0.05; ***p-value <0.001; ****p-value <0.0001.

**Abbreviations**: R5, resistance at 5 Hz; X5, reactance at 5 Hz; R20, resistance at 20 Hz; Fres, resonant frequency; R5-R20, the differences between R5 and R20.

**Table 3** The Discriminative Ability of IOS and FeNO, Alone or in Combination, Against Uncontrolled Asthma

| Variables | Cutoff | AUC | AUC 95% CI | Sensitivity | Specificity | PLR | NLR | PPV | NPV |
|---|---|---|---|---|---|---|---|---|---|
| R5 | 1.29 | 0.74 | 0.66–0.82 | 0.62 | 0.86 | 4.36 | 0.44 | 0.81 | 0.68 |
| X5 | −0.62 | 0.63 | 0.54–0.71 | 0.28 | 0.97 | 7.90 | 0.74 | 0.88 | 0.56 |
| R20 | 0.89 | 0.59 | 0.50–0.67 | 0.43 | 0.80 | 2.15 | 0.71 | 0.68 | 0.58 |
| R5-R20 | 0.46 | 0.72 | 0.64–0.80 | 0.59 | 0.80 | 2.96 | 0.50 | 0.75 | 0.66 |
| Fres | 22.28 | 0.71 | 0.64–0.79 | 0.72 | 0.71 | 2.45 | 0.39 | 0.71 | 0.71 |
| FeNO | 17.50 | 0.88 | 0.84–0.93 | 0.73 | 0.89 | 6.91 | 0.29 | 0.87 | 0.76 |
| R5+FeNO | – | 0.91 | 0.87–0.96 | 0.87 | 0.85 | 5.70 | 0.15 | 0.85 | 0.86 |
| X5+FeNO | – | 0.91 | 0.87–0.95 | 0.89 | 0.78 | 4.00 | 0.13 | 0.80 | 0.88 |
| R20+FeNO | – | 0.88 | 0.84–0.93 | 0.78 | 0.87 | 6.02 | 0.25 | 0.85 | 0.79 |
| R5-R20+FeNO | – | 0.92 | 0.87–0.96 | 0.88 | 0.84 | 5.36 | 0.13 | 0.84 | 0.87 |
| Fres+FeNO | – | 0.91 | 0.87–0.95 | 0.78 | 0.94 | 13.24 | 0.23 | 0.93 | 0.80 |

**Notes**: Cut-points of R5, X5, R20, and R5-R20 are kPa/(L·s), cut-point of Fres is L/s and cut-point of FeNO is ppb. The cut-points were selected by maximizing the total of sensitivity and specificity.

**Abbreviations**: R5, resistance at 5 Hz; X5, reactance at 5 Hz; R20, resistance at 20 Hz; Fres, resonant frequency; R5-R20, the differences between R5 and R20; AUC, area under the curve; CI, confidence interval; PLR, positive likelihood ratio; NLR, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.

sensitivity and specificity of 0.59 and 0.80, respectively. R20 had the lowest AUC of 0.59 with a sensitivity and specificity of 0.43 and 0.80, respectively. The AUC for FeNO alone was 0.88 (95% CI 0.84–0.93) with a cutoff value of 17.50 ppb, sensitivity, and specificity of 0.73 and 0.89, respectively. The AUCs of IOS parameters combined with FeNO were significantly increased, with the highest AUC of 0.92 (95% CI 0.87–0.96) for R5-R20+FeNO, and with a sensitivity and specificity of 0.88 and 0.84.

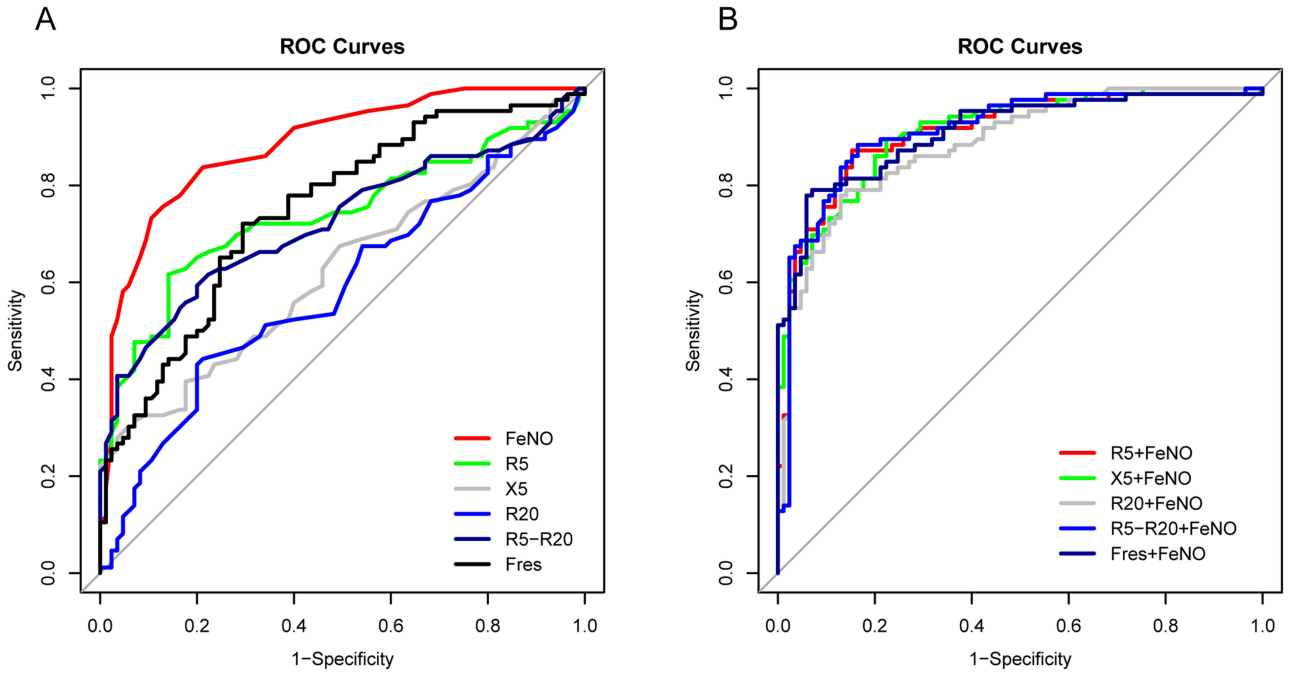


**Figure 2** The ROC curves of IOS and FeNO alone (**A**) or in combination (**B**) predicting uncontrolled asthma.

**Abbreviations**: R5, resistance at 5 Hz; X5, reactance at 5 Hz; R20, resistance at 20 Hz; Fres, resonant frequency; R5-R20, the differences between R5 and R20; ROC, receiver operating characteristic.

## Discussion

In this study, we have observed significant differences in IOS parameters and FeNO in relation to asthma control among preschool children and established cut-points to predict uncontrolled asthma. Total airway resistance (R5) and small airway resistance (R5-R20) performed well, with AUCs exceeding 0.70. FeNO might be the best index to predict asthma control and adding any of IOS index increased moderately the AUCs. Our results suggest that combining IOS and FeNO has potential clinical value for uncontrolled asthma in preschool children.

Peripheral small airway pathology has been strongly associated with asthma control, presenting a potential therapeutic target for asthma.[32] The dynamic monitoring of changes in peripheral airway resistance in children could aid in adjusting treatment strategies. However, spirometry exhibits certain limitations in monitoring peripheral airway resistance in children. Some individuals with asthma might not be diagnosed early due to normal pre- and post-bronchodilator spirometry,[33] and in some cases, they may even be inaccurately assessed for asthma control.[10] The interpretation of spirometry results for airflow obstruction also varies widely among different lung function laboratories.[34] Additionally, spirometry usually requires the patient to be coordinated in performing maximal forced expiratory maneuvers and is therefore suitable for children over 6 years of age and of limited value for poorly coordinated preschoolers. Therefore, there is a need for additional simple tests to assess peripheral airway resistance in asthmatic children, especially in preschoolers. IOS might detect alterations in airway mechanics that not reflected by spirometry.[35] Studies have indicated that IOS might be more sensitive than effort-dependent forced expiratory flow between 25% and 75% ($FEF_{25\%–75\%}$) in detecting small airway dysfunction.[36] In comparison to spirometry, IOS required fewer maneuvers, less execution time, and was considered less challenging by asthmatic children.[37] Consequently, our study aimed to compare differences in IOS metrics between controlled and uncontrolled asthma groups of preschoolers, exploring the value of IOS in predicting uncontrolled asthma.

In this study, we compared the value of five variables from the IOS (R5, X5, R20, R5-R20, Fres,) in differentiating asthma control. The IOS indicators (R5, X5, R5-R20, and Fres) were significantly higher in the uncontrolled asthma group compared to the controlled asthma group, except for R20. This suggests that the pathological changes in the uncontrolled asthma group were primarily in the peripheral airways rather than in the large airways. IOS measures the impedance of the respiratory system, and can be divided into resistive forces (resistance of the respiratory system not only total airway resistance) and reactive forces (product of the respiratory system compliance and inertance).[13] In general, R5 reflects total airway resistance, R20 reflects proximal airway resistance, R5-R20 reflects small airway resistance, and X5 and Fres reflect peripheral airway obstruction.[13] Peripheral airway impairment, as defined by IOS reference values rather than central airway markers (R20), consistently correlated with the risk of uncontrolled asthma.[9] This aligns with previous findings indicating that peripheral airway resistance assessed by IOS was associated with asthma control in children,[17,31,32,38–40] even when children exhibited normal spirometry.[10] However, some studies have reported no significant differences in IOS indicators between controlled and uncontrolled asthma groups in preschoolers.[41] Further studies are necessary to validate the predictive accuracy of IOS for uncontrolled asthma. On the other hand, our study showed that there was no statistically significant difference in IOS measurements between the controlled asthma group and the healthy control group, thus portraying the efficacy of asthma treatment in improving lung function.

FeNO levels can reflect eosinophilic airway inflammation, and the recommended FeNO threshold for children with eosinophilic asthma younger than 12 years was 20 ppb.[42] In our study, the median levels of FeNO were 23 and 11 ppb in the uncontrolled asthma and controlled asthma group, respectively. The AUC of FeNO was 0.88, with a cutoff value of 17.50 ppb, sensitivity, and specificity of 0.73 and 0.89, respectively, suggesting the FeNO index might be a good index to predict asthma control in preschool children. Research has indicated that higher FeNO levels could elevate the risk of long-term loss of control in well-controlled children with mild to moderate asthma.[43] In pediatric asthma patients, high FeNO levels were associated with increased symptom severity and poor asthma control, and FeNO levels ≥80 ppb could be used as an objective indicator of severe asthma.[44] However, the relationship between asthma control and FeNO remains controversial. A cross-sectional observational study of children (aged 6–18 years) with asthma who underwent a comprehensive assessment of asthma control found poor agreement between FeNO and clinical assessment of asthma

control.[45] In another study, there was no FeNO cut-off that had a reasonable combination of sensitivity and specificity to differentiate between controlled and uncontrolled asthma.[46] The clinical relevance of FeNO for asthma management may be enhanced by considering asthma phenotypes and age-related FeNO thresholds.[47] Furthermore, FeNO levels are influenced by numerous factors and must be interpreted in a clinical context. In addition, we found a statistically significant difference in FeNO between the controlled asthma group and the healthy control group. This might be related to the presence of more allergic phenotypes and short duration of anti-asthma treatment in the asthma group. Further long-term follow-up is needed to explore the differences in FeNO levels between the controlled asthma group and the healthy population.

Our study determined the cut-off values for identifying uncontrolled asthma by using the absolute values of five IOS metrics. In our study, total airway resistance R5 at a cutoff value of 1.29 kPa/(L·s) and small airway resistance R5-R20 at a cutoff value of 0.46 kPa/(L·s), had the highest AUC of 0.74 and 0.72, respectively. The proximal airway resistance R20 index had the lowest AUC (only 0.59), further indicating a focus of asthma pathologic changes on peripheral airway resistance. The AUCs of all IOS parameters combined with FeNO were significantly increased, with the highest AUC of 0.92 (95% CI 0.87–0.96) for R5-R20+FeNO, and with a sensitivity and specificity of 0.88 and 0.84, suggesting that FeNO combined with any of IOS metrics, especially the R5-R20, could increase moderately the predictive value of uncontrolled asthma in preschool children.

The optimal predictive parameters for IOS in uncontrolled asthma may vary across studies. R5-R20 has been proposed as the best predictor in several studies.[10,32,38,48] Previous studies found that R5-R20 at a cutoff value of 1.5 cm $H_2O$/(L·s) predicting uncontrolled asthma in children had an AUC of 0.86 and sensitivity and specificity of 0.82 and 0.84.[38] In asthmatic children with normal spirometry, the AUC of R5-R20 for predicting uncontrolled asthma could be as high as 0.81, and the AUC was even higher in combination with FeNO.[10] Another study suggested that the AUC of X5 combined with FeNO was as high as 0.87, surpassing that of a single indicator.[31] However, it was also observed that X5 appeared most robust to identify peripheral airway impairment but the AUCs for all IOS parameters were less than 0.70 to identify poor controlled asthma.[39] In summary, the predictive value of the IOS index for uncontrolled asthma in children is not yet standardized, and the combination with FeNO may emerge as a promising predictive tool, although studies on the combined model remain limited. Further large-sample, multicenter, and multifactorial studies are necessary to confirm the reliability and application value of the combined model.

On the other hand, several studies have demonstrated the potential advantage of combining both spirometry and oscillometry measurements in fully characterizing airflow limitation in moderate-to-severe asthma.[49] Combining spirometry with oscillometry could be more clinically useful in better recognizing the magnitude of uncontrolled asthma, than by either pulmonary function test alone.[50] Among children aged 6–18 years with asthma, IOS values (R5, X5, and Fres) showed a moderate correlation with spirometry values.[51] However, the idea of combining IOS with spirometry in 3–6 years old preschoolers presents challenges and requires overcoming the uncooperative nature of young children. Therefore, this study proposes that the joint analysis of simple and feasible IOS and FeNO may be more suitable for the periodic assessment of preschool children and may provide a reference point for primary care pediatricians.

However, this study has several limitations. The absence of the indicator AX in our study's IOS parameters, potentially a crucial predictor,[32,38] is attributed to limitations in instrumentation and equipment. Nevertheless, we believe that the lack of AX data can be compensated for by the evaluation of peripheral airway resistance using other IOS parameters. Another potential limitation is the relatively small number of healthy controls, which may not help detect more subtle differences between healthy children and controlled asthma group patients. Additionally, limited by the ability of preschoolers to cooperate, spirometry was not measured in this study and the follow-up period was not long enough. Larger sample sizes, multifactorial analyses, and longer follow-up are needed to further explore the value of IOS combined with FeNO in preschoolers.

## Conclusions

In this study, we have observed significant differences in IOS and FeNO between controlled asthma group and uncontrolled asthma group in preschoolers. Total airway resistance (R5) and small airway resistance (R5-R20) had predictive value. FeNO might be the best predictor of asthma control in preschool children, and adding any of IOS

metrics increased moderately the predictive value. In clinical practice, the joint analysis of IOS and FeNO may assist pediatricians in early identification of the risk of uncontrolled asthma, allowing for timely adjustments. Future studies should focus on larger sample sizes, prolonged follow-up, and multifactorial analyses.

## Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Institutional Review Board at Hangzhou Children's Hospital (2021-14). Informed consent was obtained from all the parents or guardians of minors. All research activities were conducted in accordance with hospital's guidelines and requirements. The study complied with the Declaration of Helsinki.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; have agreed on the journal to which the article has been submitted; have agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage, and agree to be accountable for the contents of the article.

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## Disclosure

The authors declare that they have no conflicts of interest in this work.

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