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ORIGINAL RESEARCH

Predictive Value of Impulse Oscillometry Combined with Fractional Expiratory Nitric Oxide Test for Asthma in Preschool Children

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Objective: Prediction of asthma in preschool children is challenging and lacks objective indicators. The aim is to observe and analyze the variances between impulse oscillometry (IOS) and fractional expiratory nitric oxide (FeNO) in preschool children with wheezing, establish a joint prediction model, and explore the diagnostic value of combining IOS with FeNO in diagnosing asthma among preschool children.

Patients and methods: This study enrolled children aged 3–6 years with wheezing between June 2021 and June 2022. They were categorized as asthmatic (n=104) or non-asthmatic (n=109) after a 1-year follow-up. Clinical data, along with IOS and FeNO measurements from both groups, underwent univariate regression and multiple regression analyses to identify predictive factors and develop the most accurate model. The prediction model was built using the stepwise (stepAIC) method. The receiver operating characteristic curve (ROC), calibration curve, Hosmer-Lemeshow test, and decision curve analysis (DCA) were employed to validate and assess the model.

Results: During univariate analysis, a history of allergic rhinitis, a history of eczema or atopic dermatitis, and measures including FeNO, R5, X5, R20, Fres, and R5-R20 were found to be associated with asthma diagnosis. Subsequent multivariate analysis revealed elevated FeNO, R5, and X5 as independent risk factors. The stepAIC method selected five factors (history of allergic rhinitis, history of eczema or atopic dermatitis, FeNO, R5, X5) and established a prediction model. The combined model achieved an AUROC of 0.94, with a sensitivity of 0.89 and specificity of 0.88, surpassing that of individual factors. Calibration plots and the HL test confirmed satisfactory accuracy.

Conclusion: This study has developed a prediction model based on five factors, potentially aiding clinicians in early identification of asthma risk among preschool children.

Keywords: asthma, impulse oscillometry, fractional expiratory nitric oxide, prediction model, preschool children

Introduction

Bronchial asthma is a prevalent and complex heterogeneous disease characterized by chronic airway inflammation, airway hyperresponsiveness, and reversible airflow limitation.[1] Clinical manifestations include wheezing, shortness of breath, chest tightness, and cough. This chronic respiratory condition poses a significant threat to children's health, resulting in a substantial disease burden.[2] Chronic airway inflammation is typically characterized by eosinophilic activity and allergic inflammation. Airway remodeling is a common feature of asthma, exhibiting typical pathology that can develop in preschoolers aged 1–3 years.[3] Asthma typically initiates early in life, with approximately 50% of children experiencing symptoms like wheezing in the first six years. About 40% continue to have persistent wheezing in late childhood, leading to compromised lung function.[4] The diagnosis of asthma includes various combinations of characteristic symptoms, reversible airflow limitation, and inflammation that may be present differently in individuals.

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Relying on wheezing phenotypes to predict the risk of asthma in preschool children in clinical practice is very difficult, and the underdiagnosis rate of asthma in urban Chinese children has been found to be as high as 30%.[5] Spirometry can provide evidence of reversible airflow limitation and is an important clinical tool for the diagnosis and monitoring of asthma. However, spirometry requires a forced expiratory maneuver, and its accuracy and reproducibility rely on the patient's level of cognition and effort. It is usually applied to older children over 6 years of age and has limited diagnostic value for preschoolers with poor comprehension and low cooperation. Clinical tools may predict asthma risk in children, but a negative asthma predictive index result does not exclude the possibility of developing asthma later in life.[6] Therefore, there is an urgent need to explore objective prediction models for asthma in preschool children.

Impulse oscillometry (IOS) is a simple, non-invasive method using forced oscillation technology that requires minimal patient cooperation and can be used for spirometry in preschool children.[7] The IOS utilizes externally applied pressure signals and flow rates to generate resistance (Rrs) and reactance (Xrs) between 5 and 20 Hz to assess lung function, reflecting the physiological characteristics of different cases of asthma.[8] In general, reactance at 5 Hz (X5) and reactance area (AX) reflect peripheral airway obstruction, resistance at 5 Hz (R5) reflects proximal and distal airways obstruction, and resistance at 20 Hz (R20) represents proximal airways resistance; the resistance of small airways can be calculated from R5-R20.[8] In comparison to spirometry, IOS requires fewer maneuvers, less execution time, and is more sensitive in differentiating asthmatic from non-asthmatic children.[9,10] According to the recommendations of the European Respiratory Society, IOS can be measured starting at 2 years of age.[11] In conclusion, IOS has important clinical value in the diagnosis of asthma and monitoring of pulmonary function in preschool children.[12–15]

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.[16] FeNO is a good surrogate marker for eosinophilic airway inflammation.[17] 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.[18–20] According to the ATS guidelines, FeNO > 35 ppb in children can be used to indicate eosinophilic inflammation and may be responsive to corticosteroids in symptomatic patients, whereas in the population of eosinophilic asthmatics, FeNO > 25 ppb may have some diagnostic properties for asthma but should be interpreted cautiously with reference to the clinical context.[21] However, FeNO could be affected by a number of factors, and its use as a diagnostic indicator of asthma was controversial.[22] In conclusion, the potential of this technology has not been fully evaluated and more studies are needed to evaluate FeNO-based management in appropriate patient and clinical settings.

Combined spirometry and FeNO could enhance the accuracy of asthma diagnosis in children aged 8–16 years.[23] However, the diagnostic value of combining IOS with FeNO for asthma in preschool children has not been fully investigated. Currently, the combined IOS and FeNO test was mainly used to assess asthma control and the risk of acute exacerbations in preschool children. It is also used to predict cough variant asthma in preschool children with chronic cough.[24–27]

In this study, our objectives were to observe and analyze the distinctions between IOS and FeNO in preschool children with wheezing, establish a joint prediction model, and explore the diagnostic value of combining IOS with FeNO in preschool children with asthma.

Methods

Study Participants

This study was conducted at a specialized children's hospital in Zhejiang Province, China, from June 2021 to June 2022. Approval for the study was obtained from the Ethics Committee of the Institutional Review Board at Hangzhou Children's Hospital (2021–14).

Inclusion Criteria

The inclusion criteria for participants were as follows: 1) aged 3 to 6 years (both sexes), 2) experiencing wheezing symptoms, 3) successful completion of IOS and FeNO tests, and 4) successful one-year follow-up.

Exclusion Criteria

1) Use of oral or intravenous glucocorticoids for at least 4 weeks prior to the study, 2) presence of other respiratory diseases such as bronchial foreign bodies, bronchopulmonary dysplasia, pneumonia, and lung malformations, 3) existence of other underlying diseases such as congenital heart disease, immunodeficiency, and neurologic diseases, 4) failure in IOS and FeNO tests, and 5) inability to complete the one-year follow-up.

Grouping Criteria

The children were categorized into asthma and non-asthma groups according to the diagnostic recommendations of the modified asthma predictive index (mAPI).[28] The mAPI is considered positive when a patient has had four wheezing episodes in a year, referred to as the primary threshold. Additionally, the patient also must meet the secondary threshold which requires the presence of at least one major criterion or at least two minor criteria. The major criteria include parental history of asthma, physician diagnosed atopic dermatitis, and allergic sensitization to at least 1 aeroallergen. The minor criteria comprise wheezing unrelated to colds, peripheral blood eosinophils≥4%, and allergic sensitization to milk, egg, or peanuts.

Impulse Oscillometry

The instrument (MasterScreen IOS, Jaeger, German) was operated by a professional technician at baseline according to the American Thoracic Society/European Respiratory Society statement.[29] The child was seated or stood in a natural or slightly tilted head position, with tightly clenched teeth in the mouth clip. The operator gently pressed both sides of the child's cheeks, instructing them to breathe calmly and evenly, avoiding air leakage, vocalization, and swallowing during testing process. Data collection commenced after achieving stable breathing and a stabilized baseline, with a testing time of not less than 30 seconds and at least three recorded respiratory cycles. 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).

FeNO Measurement

The instrument used (Sunvou-CA2122, Jiangsu, China) was operated by a professional technician at baseline according to the ATS/ERS guidelines.[30] Inhaled corticosteroids (ICS) and short-acting beta-agonists were withheld for 24 h prior to measurements. Patients were instructed to abstain from eating, drinking, and exercise for 2 hours before FeNO measurements. Online tidal gasometry was conducted in cooperative children. Seated upright, the child took a deep breath to evacuate the lungs, held a disposable bacterial filter in the mouth, and maintained steady breathing (expiratory flow rate of 50 mL/s) for at least >4 seconds, as measured by the analyzer. For children with poor cooperation, the offline mode was selected. In this mode, the child inhaled deeply from a gas reservoir bag without nitric oxide, exhaled into a specialized gas collection bag, and finally underwent testing with a meter. The parameter was expressed in parts per billion (ppb).

Sample Size

The sample size calculation module in the PASS software was utilized for comparing two ROC curves. The anticipated area under the curve (AUC) for the joint model and FeNO was 0.86 and 0.72, respectively.[31] Considering a significance level of alpha=0.05 (two-tailed), a power of 80%, and a 1:1 ratio of negative to positive subjects, each test and control group required 46 cases. Accounting for a 20% dropout rate, a total of 58 negative and 58 positive subjects were needed.

Clinical Data Collection

Age, sex, height, weight, history of allergic rhinitis, history of eczema/atopic dermatitis, and family history of allergy were collected from the children at baseline. Family history of allergy refers to a history of allergic rhinitis, eczema, urticaria, food allergy, asthma, and other allergic conditions in the patient's first-degree family members.

Statistical Analysis

Continuous variables were expressed as mean ± SD or median (P25, P75), with group comparisons conducted using t-tests and Mann–Whitney tests. Count data were presented as cases (%), and group comparisons were made using the chi-square test or Fisher's exact probability method. A p-value < 0.05 was considered statistically significant. Univariate regression and multiple regression analysis were performed on the clinical data, IOS, and FeNO of the two groups. The prediction model was built using the stepwise (stepAIC) method in R (4.2.2) and its discrimination ability was assessed using the area under the receiver operating characteristic curve (AUROC). Area under curve (AUC) >0.7 was considered to be of clinical diagnostic value. Calibration ability was tested using a calibration curve and the Hosmer-Lemeshow (HL) test. Decision curve analysis (DCA) was employed to evaluate its clinical efficacy.

Results

Demographic Characteristics and IOS/FeNO Parameters of the Study Population

This study finally included 213 wheezing children, with a median age of 53 months, comprising 126 males and 87 females. Following a one-year follow-up by specialized respiratory physicians, 104 children received a final diagnosis of asthma, while 109 children were diagnosed with non-asthma conditions. A comparison of demographic characteristics and IOS/FeNO parameters between asthmatic and non-asthmatic groups is presented in Table 1. There were no statistically significant differences observed in age, sex, height, and weight between the two groups, indicating comparable baseline populations. Notably, the asthma group exhibited significantly higher occurrences of a history of allergic rhinitis (p=0.047) and a history of eczema or atopic dermatitis (p=0.031) compared to the non-asthma group. Additionally, R5, X5, R20, R5-R20 and Fres parameters were higher in the asthma group (all p<0.001). The median level of FeNO was significantly higher in the asthma group at 16.00 (11.00, 24.00) ppb than in the non-asthma group at 7.00 (5.00, 11.00) ppb.

Multivariate Regression Analysis and Optimal Model for Predicting Asthma in Preschool Children

Demographic characteristics and IOS/FeNO parameters of the two groups were subjected to univariate regression analysis (Table 2). This analysis revealed that a history of allergic rhinitis, a history of eczema or atopic dermatitis, R5, X5, R20, Fres, R5-R20, and FeNO were associated with the diagnosis of asthma. Subsequently, these factors underwent multivariate logistic regression and were illustrated in Table 3. Elevated R5, X5, and FeNO were identified as

Table 1 Demographic Characteristics and IOS/FeNO Parameters of the Study Population

Variables	Asthma (n=104)	Non-Asthma (n=109)	*p*-value
Age, month, M (P25, P75)	55.00(47.25, 64.00)	49.00(46.00, 63.00)	0.082
Male, n (%)	62(59.62)	64(58.72)	0.894
Height, cm, M (P25, P75)	107.65(102.43, 112.80)	106.1(101.85, 112.60)	0.628
Weight, Kg, M (P25, P75)	18.00(16.00, 19.75)	18.00(16.00, 20.85)	0.751
Allergic rhinitis history, n (%)	71(68.27)	60(55.05)	0.047
Eczema or atopic dermatitis history, n (%)	64(61.54)	51(46.79)	0.031
Allergic family history, n (%)	58(55.77)	48(44.04)	0.087
R5, % predicted, M (P25, P75)	139.60 (125.50, 154.65)	105.80 (96.20, 115.80)	<0.001
X5, % predicted, M (P25, P75)	121.70 (94.43, 160.83)	100.30 (74.35, 122.80)	<0.001
R20, % predicted, M (P25, P75)	94.60 (82.50, 103.10)	82.10 (71.00, 89.90)	<0.001
Fres, l/s, M(P25, P75)	23.49 (21.39, 27.00)	21.60 (19.83, 23.92)	<0.001
R5-R20, kpa/(l/s), M (P25, P75)	0.45 (0.26,0.63)	0.31 (0.20,0.43)	<0.001
FeNO, ppb, M (P25, P75)	16.00 (11.00, 24.00)	7.00 (5.00, 11.00)	<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.

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 2 Univariate Regression Analysis of All Variables

Variables	OR	95% CI	*p*-value
Age	1.02	0.99–1.05	0.093
Sex	1.04	0.60–1.79	0.894
Height	1.01	0.97–1.05	0.637
Weight	0.97	0.89–1.05	0.436
Allergic rhinitis history	1.78	1.00–3.07	0.048
Eczema or atopic dermatitis history	1.82	1.06–3.14	0.032
Allergic family history	1.60	0.93–2.75	0.088
R5	1.11	1.08–1.14	<0.001
X5	1.02	1.01–1.03	<0.001
R20	1.06	1.04–1.08	<0.001
Fres	1.12	1.05–1.20	0.001
R5-R20	13.16	3.50–49.49	<0.001
FeNO	1.14	1.08–1.19	<0.001

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 Multivariate Regression Analysis of the Variables

Variables	OR	95% CI	*p*-value
Allergic rhinitis history	2.29	0.89–5.88	0.086
Eczema or atopic dermatitis history	2.20	0.87–5.59	0.098
R5	1.09	1.04–1.13	<0.001
X5	1.02	1.01–1.03	0.016
R20	1.02	0.97–1.07	0.516
Fres	0.93	0.81–1.07	0.312
R5-R20	1.95	0.04–93.74	0.312
FeNO	1.09	1.04–1.15	0.001

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.

independent risk factors for asthma diagnosis ($p < 0.05$). A stepAIC function was used to perform a stepwise model selection using AIC (Akaike information criterion). Finally, a model including five variables, history of allergic rhinitis, history of eczema or atopic dermatitis, FeNO, R5 and X5, was constructed as the optimal predictive model. The model equation is as follows: Logit(P)=−14.3549+0.7602*History of allergic rhinitis+0.7401*History of eczema or atopic dermatitis+0.0928*FeNO+0.0863*R5+0.0148*X5.

Validation of the Prediction Model

Initially, we analyzed the diagnostic efficacy of the prediction model and individual metrics using ROC curves (Table 4, Figure 1A). The predictive efficacy was ranked as follows: prediction model > R5 > FeNO > X5, indicating that the

Table 4 The ROC Curves of IOS/FeNO Variables and the Asthma Prediction Model

Variables	Cutoff	AUC	*p*-value	Sensitivity	Specificity	ppv	npv	kappa
FeNO	8.50ppb	0.84	<0.001	0.90	0.62	0.69	0.87	0.52
R5	119.45% predicted	0.91	<0.001	0.89	0.84	0.84	0.88	0.72
X5	145.95% predicted	0.69	<0.001	0.33	0.99	0.97	0.61	0.32
Model	-	0.94	<0.001	0.89	0.88	0.88	0.90	0.78

Abbreviations: R5, resistance at 5 Hz; X5, reactance at 5 Hz; AUC, area under curve; PPV, positive predictive value; NPV, negative predictive value.

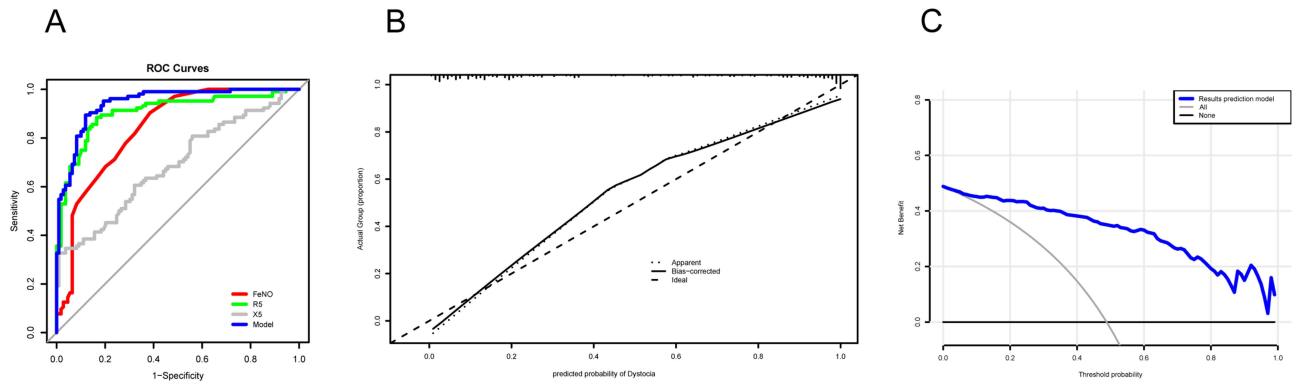

Figure 1 Validation of the prediction model. (**A**) ROC curves for FeNO, R5, X5, and the prediction model. (**B**) Calibration curve of the prediction model. (**C**) Decision curve analysis of the prediction model.
Abbreviations: R5, resistance at 5 Hz; X5, reactance at 5 Hz.

predictive value of the model exceeded that of any single indicator. The combined model achieved an AUC of 0.94, with a sensitivity of 0.89 and specificity of 0.88. The positive predictive value (PPV) and negative predictive value (NPV) were 0.88 and 0.90, respectively. The Hosmer-Lemeshow test chi-square value of 11.788 (p>0.05) indicated that the model demonstrated a high degree of calibration. In the calibration curve (Figure 1B), the trajectories of the three curves (the prediction result curve, the error correction curve, and the ideal curve) essentially overlapped, indicating satisfactory accuracy of the model. To assess the clinical usefulness of the model, DCA was implemented (Figure 1C), revealing positive net benefits. R5 had an AUC of 0.91 at a cutoff value of 119.45% predicted, with a sensitivity and specificity of 0.89 and 0.84. FeNO had an AUC of 0.84 at a cutoff value of 8.50 ppb, with a sensitivity and specificity of 0.90 and 0.62, respectively. The AUC of X5 value was only 0.69.

Discussion

The diagnosis of asthma in children is based on characteristic symptom patterns and evidence of reversible airflow limitation. The assessment and diagnosis of preschool children pose challenges due to atypical symptoms and low cooperation with pulmonary function tests, leading to a lack of standardized diagnostic criteria. This study included 213 preschool children with wheezing. Significant differences were found between the IOS and FeNO indices in both the asthma and non-asthma groups through multivariate analysis, a joint model for predicting asthma in preschool children was identified, with sensitivity and specificity exceeding 0.8. Our results findings indicate that the combination of IOS and FeNO holds predictive value for asthma in preschoolers, aiding clinicians in objectively assessing the risk.

In the present study, children in the asthma group exhibited a higher prevalence of a history of allergic rhinitis and a history of eczema or atopic dermatitis. This fits well with the natural history of asthma and allergies in children. A meta-analysis revealed a significant association between atopic dermatitis and a family history of asthma, increasing the likelihood of developing asthma before school age.[32] Atopic reactions were observed in the majority of children with asthma aged over 3 years. Allergen sensitization, particularly multiple sensitizations early in life, emerged as one of the most critical risk factors for the development of asthma.[33] The Global Initiative for Asthma (GINA) has identified personal food allergies or atopic dermatitis, family history of atopic disease or asthma, as risk factors for the development of asthma.[1]

As preschoolers are often less cooperative in completing spirometry, clinical practice has started experimenting with using IOS measurements to assess airway conditions in this age group, as it requires only minimal cooperation. IOS evaluates the mechanical properties of the respiratory system by measuring respiratory system resistance and reactance. This allows for a more physiological, quicker, and easier assessment of lung function compared to spirometry.[34] It had been suggested that the addition of IOS to spirometry in the guidelines could better identify uncontrolled asthma, future exacerbations, and potential targeted therapies.[35] In this study, the IOS indicators R5% predicted, X5% predicted, R20% predicted, Fres, and R5-R20 were significantly higher in the asthma group compared to the non-asthmatic group, and

multivariate analysis revealed that R5 and X5 may be independent risk factors for asthma in preschool children. R5 had an AUC of 0.91 at a cutoff value of 119.45% predicted, with a sensitivity and specificity of 0.89 and 0.84, but the AUC of X5 value was only 0.69. 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.[8] Previous studies have shown that R5, AX, and R5-R20 were higher in the asthma group than in the control group, while X5 was lower in the control group.[36] R20 was also shown to be increased in the asthma group compared to the healthy control group.[37] In addition, bronchodilator response (BDR) assessed using IOS can be used to identify patients with asthma. When comparing percent change in pre- and post-BDR, there was a statistically significant difference in the percent change of R5, R10, X5, and AX, ROC found that % change R10 had the highest AUC (0.71), but the AUC for both % change R5 and % change X5 was less than 0.7.[9] Moreover, spirometry reversibility could be detected by ≤-22.34 and ≤-39.05 cut-off values of ΔR5 and ΔAX, respectively.[38] Another study suggested a decrease of 25.7% in R5 and an increase of 25.7% in X5 as diagnostic threshold for BDR.[39] These studies suggest that BDR based on IOS better differentiates asthmatic from healthy subjects than BDR based on spirometry, possibly because IOS reflects changes in the small airways, where asthmatic changes occur earlier, before the large airway abnormalities characterized by spirometry.[40] The traditional spirometry was of limited value in assessing peripheral airway injury.[41] In a follow-up study, we will also further evaluate the value of IOS in asthma BDR in preschool children to enrich the clinical prediction model.

FeNO levels can reflect eosinophilic airway inflammation, and FeNO > 25 ppb may have some diagnostic value in a population of patients with eosinophilic asthma.[21] A systematic analysis evaluating FeNO for moderate diagnostic performance in childhood asthma.[42] In this study, FeNO levels were significantly higher in the asthma group with a median of 16 ppb, and the AUC for predicting asthma was 0.84 at a cutoff value of 8.50 ppb, with a sensitivity and specificity of 0.90 and 0.62, respectively. Although the median level of FeNO in the asthma group of this study was low, below 25 ppb, it was similar to the findings of previous studies in preschool children. Previous studies have found that median FeNO levels in asthmatic children aged 3–47 months were significantly higher at 10.5–11.7 ppb than in non-asthmatic children at 6.5–7.4 ppb.[18,43] The predictive value of FeNO in children with asthma varies widely between studies. At a cut-off of 22 ppb, the sensitivity and specificity of FeNO for diagnosing asthma in children aged 8–16 years were 0.57 and 0.87, respectively.[44] However, at a cut-off of 19 ppb, the sensitivity and specificity of FeNO for diagnosing mild asthma in children aged 6–14 years were 0.91 and 0.87, respectively.[45] Another study suggested that FeNO levels were significantly higher in asthmatic children (9.6 ppb) than in healthy children (5.8 ppb), and that allergic sensitization was most closely related to FeNO, a cutoff value of 20.4 ppb was associated with high diagnostic specificity (0.97) and low sensitivity (0.41).[46] In addition, atopy and allergic rhinitis were independently associated with increased FeNO level, only among patients with atopy and allergic rhinitis FeNO level (above 23 ppb) was associated with asthma diagnosis, with a sensitivity of 0.90 (95% CI: 0.68–0.98) and a specificity of 0.52 (95% CI: 0.42–0.61).[47] These differences may be related to different thresholds and reference standards, as well as to the fact that FeNO is affected by a number of factors. It has been suggested that rather than replacing current physiological testing, FeNO should be used in conjunction with testing for reversible or variable airflow obstruction to support the diagnosis of asthma.[48]

In this study, we constructed a prediction model based on the AIC guidelines incorporating five factors (history of allergic rhinitis, history of eczema or atopic dermatitis, FeNO, R5 and X5), and the ROC curves suggested that the AUC could be as high as 0.94, with sensitivity and specificity of 0.89 and 0.88, respectively, which is superior to single indicators and has good discriminatory ability, calibration and clinical utility. Previous studies have found that the "R20 +AX+FeNO" model could be used for the diagnosis of asthma in preschool children, with an AUC of 0.86, a sensitivity of 0.79, and a specificity of 0.77.[31] In addition, IOS in combination with FeNO could predict cough-variant asthma in preschool children, with AUCs of 0.78 and 0.66 for FeNO alone and X5 alone, respectively, whereas FeNO (cutoff value of 18 ppb) in combination with X5 (cutoff value of −4.15cmH 2 O/(l/s)) reached an AUC of 0.81.[27] However, there is still limited information on the predictive model of IOS combined with FeNO on asthma in preschool children. Therefore, our study suggests that the combined IOS and FeNO model holds potential as a valuable tool in assisting the diagnosis of asthma in preschool children in clinical practice. Particularly, multiple follow-ups of children with high-risk factors within the same hospital unit can have practical applications for their diagnosis and subsequent management.

However, it's worth noting that model parameters and cutoff values lack standardization across different studies. Large-sample, multicenter studies are imperative to further establish the reliability and generalizability of the diagnostic model.

However, this study has certain limitations. The absence of the indicator AX in our study's IOS parameters, potentially a crucial predictor,[38,49] is attributed to limitations in instrumentation and equipment. Additionally, the present study is characterized by a relatively modest sample size and is a single-center study. Future multicenter studies with larger samples are essential to yield more robust and convincing results.

Conclusions

In this study, we constructed a prediction model by combining IOS and FeNO to assess the risk of asthma in preschool children with wheezing, demonstrating diagnostic superiority over individual factors. The prediction model, incorporating five factors, exhibited excellent discriminatory ability, calibration, and clinical utility. Applying the joint prediction model in clinical practice for preschool children with high-risk factors assists clinicians in early to accurate assessment of asthma risk, ultimately contributing to improved lung function and quality of life. Future studies should focus on expanding the sample size to optimize and validate the prediction model.

Ethics Approval and Consent to Participate

Our 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 participants. 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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