

Original Article

Analysis of the diagnostic value of fractional exhaled nitric oxide and IgE in children with asthma

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Abstract: Objective: The aim of the current study was to analyze the diagnostic value of fractional exhaled nitric oxide (FeNO) and IgE in children with asthma. Methods: Seventy-five children with bronchial asthma (observation group) and 50 healthy children (control group) were enrolled. The 75 children with bronchial asthma were divided into 31 cases of eosinophilic (subgroup) asthma and 44 cases of non-EOS asthma (non-EOS group). Children with bronchial asthma received routine treatment, such as anti-inflammation, anti-asthma, anti-tussive, and anti-phlegm measures. Differences in FeNO and IgE levels between the asthma and control group and between asthma subgroups were investigated before and after treatment. Effects of treatment on FeNO and IgE levels in asthma patients were observed. The relationship between FeNO levels and IgE/FEV1 in asthma patients was calculated with Pearson's analysis. ROC curve analysis was performed to examine the diagnostic performance of FeNO and IgE for asthma and EOS asthma. Results: There were significant differences in levels of FeNO and IgE between the observation group and control group before and after treatment ($P < 0.001$). After treatment, levels of FeNO and IgE in EOS and non-EOS groups were higher than those in the control group ($P < 0.001$). Levels of FEV1% were lower than those in the control group ($P < 0.001$). There were no significant differences between the subgroup and non-EOS group regarding FeNO and IgE levels before treatment ($P > 0.05$). Levels of FeNO and IgE in EOS and non-EOS children that received treatment were lower than those before treatment. FEV1% levels were higher than those before treatment ($P < 0.001$). Spearman's analysis suggested that FeNO was positively correlated with expression of IgE ($r = 0.542$, $P < 0.001$) and negatively correlated with FEV 1% ($r = -0.512$, $P < 0.001$). Expression of IgE was negatively correlated with FEV 1% ($r = -0.410$, $P < 0.001$). ROC curve analysis showed that the areas under the curve, diagnostic levels, sensitivity, and specificity levels of FeNO in the diagnosis of asthma and EOS asthma were 0.982, 32 ppb, 90.67%, and 100% and 0.724, 52.02 ppb, 51.16%, and 87.10%, respectively. Areas under the curve, diagnostic levels, sensitivity, and specificity levels of IgE in the diagnosis of asthma and EOS asthma were 0.987, 25.23 IU/mL, 98.67%, and 100%, and 0.674, 250.10 IU/mL, 95.45%, and 45.16%, respectively. Conclusion: FeNO shows high diagnostic value for children with asthma. FeNO ≥ 32 ppb indicates that children suffered from asthma. When FeNO ≥ 52 , EOS asthma and non-EOS asthma could be distinguished.

Keywords: Fractional exhaled nitric oxide (FeNO), IgE, pediatric asthma, diagnosis

Introduction

Pediatric bronchial asthma, a heterogeneous disease characterized by chronic inflammatory disorders of the airways, in which many cells and cellular elements play a role, is often accompanied by variable expiratory airflow limitations. About 70% to 80% children, aged 4 and 5, suffer from bronchial asthma, with coughing as the most common symptom [1, 2]. With changes in social and living environments and various environmental pollution, incidence rates of children with bronchial asthma have increased year by year, causing a great impact

on learning, life, physical health, and mental health levels of the children [3, 4]. Therefore, they should receive clinical treatment, aiming to prevent irreversible stenosis and remodeling of the airway.

At present, the standards for diagnosis of bronchial asthma airway inflammation are endo-bronchial biopsies or bronchoscope support tube lavage fluid. These methods have some limitations, such as complicated operations, area of trauma, and high costs, making them difficult to apply [5, 6]. Pulmonary function tests are commonly used to assess and control asth-

ma [7]. Some studies have shown no significant correlation between pulmonary function test results and airway inflammation in patients with bronchial asthma [8]. Therefore, it is necessary to find biomarkers with convenience, safety, and specificity for diagnosis of bronchial asthma.

Fractional exhaled nitric oxide (FeNO) can help identify allergic/eosinophilic inflammation, supporting a diagnosis of asthma when other objective evidence is lacking [9]. Studies have shown that detection of FeNO in patients with bronchial asthma can be used to reflect the degree of airway inflammation. During airway inflammation, activated epithelial cells increase production of NO [10]. For patients already been diagnosed with asthma, tracking FeNO levels will determine if current the management plan is working properly. FeNO testing is non-invasive, safe, and easy to operate, with high reproducibility and high compliance [11, 12]. The Global Initiative for Asthma has suggested that FeNO is the most ideal biomarker for eosinophilic airway inflammation and asthma [13]. Other studies have found that combined evaluations with FeNO and b-EOS can identify patients with frequent exacerbations, helping to stratify the appropriate therapy for type 2 inflammation-predominant severe asthma [14]. Thus, FENO and B-Eos complement each other as asthma biomarkers [15].

Bronchial asthma is the main clinical manifestation of IgE-mediated type I allergic disease. Anti-IgE antibodies are targeted therapies for bronchial asthma [16].

At present, there are no fixed standards for the diagnostic value of FeNO in children with asthma. The current study aimed to provide analysis for clinical application of FeNO.

Materials and methods

Research objects

This study analyzed the clinical data of 75 children with bronchial asthma. Of the children with bronchial asthma, aged from 1-10, 31 cases were of eosinophilic (EOS) asthma with peripheral blood of EOS% $\geq$ 3%. A total of 44 cases were non-EOS asthma with peripheral blood < 3%. Inclusion criteria: Children that met the diagnostic criteria of the 2017 Global Initiative for Asthma [17]; Accompanied by

coughing, recurrent coughing, sleep disorders, nasal flaring, and pulmonary rales; Patients with atypical symptoms, accompanied by positive bronchial provocation tests or exercise tests positive; No presence of allergic diseases; No history of glucocorticoid therapy; No history of drug allergies; No history of respiratory diseases; Complete clinical data. Exclusion criteria: Cases with wheezing, shortness of breath, or coughing caused by other diseases; Children treated with anti-IgE antibody drugs; Presence of abnormal bleeding or coagulation disorders; Cardiovascular and cerebrovascular diseases; Liver and kidney diseases; Digestive diseases; Transfers; Relatives of the children did not cooperate with the treatment; Presence of mental disorders. Healthy children aged 1-10 years with complete data were included. Children with a history of allergic rhinitis, bronchial asthma, family allergies, and acute respiratory infections before treatment were also excluded. The current study was approved by the Medical Ethics Committee of the Affiliated Renji Hospital, Shanghai Jiaotong University School of Medicine. All patients and family members provided informed consent.

Outcome measures

Children with bronchial asthma received routine treatment, including anti-inflammation, anti-asthma, anti-tussive, and anti-phlegm measures, as well as oxygen inhalation therapy. FeNO, IgE, and pulmonary function were measured before treatment and 2 weeks after treatment, aiming to analyze the diagnostic value of FeNO and IgE in children with asthma and EOS asthma.

Evaluation criteria for therapeutic effects

Therapeutic effects were divided into marked effectiveness, effectiveness, and ineffectiveness. Marked effectiveness refers to patients that were free of coughing, shortness of breath, and pulmonary rales. Moreover, the body temperature returned to normal and there were no complications. Effectiveness refers to children with coughing, shortness of breath, and pulmonary rales that were greatly improved. Ineffectiveness refers to children with coughing, shortness of breath, and pulmonary rales that remain unchanged or worsened. The total effective rate equals (marked effectiveness + effectiveness)/total number of cases * 100%.

Table 1. General information

	Control group (n = 50)	Observation group (n = 75)	χ^2/t	P
Gender [n (%)]			0.086	0.770
Male	26 (52.00)	41 (54.67)		
Female	24 (48.00)	34 (45.33)		
Age (years old)	5.13 $\pm$ 1.42	5.08 $\pm$ 1.47	0.189	0.851
Weight (kg)	35.16 $\pm$ 12.75	33.47 $\pm$ 10.68	0.797	0.427
Height (cm)	141.75 $\pm$ 18.54	143.22 $\pm$ 18.71	0.432	0.667
Course of acute disease (month)		1.92 $\pm$ 0.58		
Average course of disease (month)		4.17 $\pm$ 1.36		
Degree of disease [n (%)]				
Mild		29 (38.67)		
Moderate		37 (49.33)		
Severe		9 (11.11)		
Exposure to second-hand smoke [n (%)]				
Yes		14 (18.67)		
No		61 (81.33)		

FeNO testing

FeNO was tested by PGM-1860 type of ToxiRAE Pro EC produced by Beijing Oriental High Technology Co., Ltd. This method was in accord with the standards of the European Respiratory Society and the American Thoracic Society.

IgE testing

Peripheral blood of the subjects was collected by nurses in the early morning for examinations within 1 hour. ELISA was used to detect IgE in the peripheral blood, according to kit instructions. The IgE kit with article number YYDB-0509 was purchased from Shanghai Youyu Biological Technology Co., Ltd.

Pulmonary function testing

Pulmonary function was tested with AS-507 from Shanghai Jmmmedical Devices Co., Ltd.

Statistical analysis

Collected data was analyzed with SPSS 19.0 (Asia Analytics Formerly Spss China). Count data are expressed as [n (%)]. The ratio was compared by using χ^2 tests. Measurement data are expressed as mean $\pm$ sd. One-way analysis of variance (ANOVA) with post-hoc LSD tests were used for comparisons between groups. ROC curves were used to analyze the application value of FeNO and IgE for diagnosis of asthma in children. Correlation levels

between FeNO, IgE, and pulmonary function, before and after treatment, were analyzed with Pearson's analysis. $P < 0.05$ indicates statistical significance.

Results*General information*

There were 50 cases in the control group, including 26 boys (52.00%) and 24 girls (28.00%), aged (5.13 $\pm$ 1.42) years old, with weights of (35.16 $\pm$ 12.75) kg and heights of (141.75 $\pm$ 18.54) cm. There were 75 cases were in the observation group, including 41 boys (54.67%) and 34 girls (45.33%), aged (5.08 $\pm$ 1.47) years old, with weights of (33.47 $\pm$ 10.68) kg and heights of (143.22 $\pm$ 18.71) cm. There were no significant differences in gender, age, heights, and weights ($P > 0.05$) in the two groups. The average course and degree of the disease, in the observation group, is described in **Table 1**.

Therapeutic effects

Results, after treatment, showed that the cure rate was 28.00% (31 cases). The effective rate was 52.00% (39 cases), the total effective rate was 80%, and the ineffective rate was 20%.

FeNO testing

Before treatment, levels of FeNO in the control group were (17.13 $\pm$ 6.07) ppb. EOS asthma in

Table 2. FeNO test (ppb)

	Control group	EOS asthma	Non-EOS asthma	F value	P value
Before treatment	17.13 ± 6.07	69.33 ± 21.84 ^{#, &}	53.45 ± 18.64 ^{#, &}	117.376	< 0.001
After treatment	16.83 ± 5.99	49.75 ± 18.59 ^{*, #}	38.91 ± 17.38 ^{*, #, &}	56.595	< 0.001

Note: *indicates compared with the same group before treatment; $P < 0.05$, #indicates compared with the control group at the same time point $P < 0.05$, &indicates compared with subgroup at the same time point $P < 0.05$.

Table 3. IgE test (IU/mL)

	Control group	EOS asthma	non-EOS asthma	F value	P value
Before treatment	21.43 ± 10.38	225.88 ± 98.26 [#]	163.14 ± 61.25 ^{#, &}	114.679	< 0.001
After treatment	22.18 ± 10.42	173.34 ± 94.17 ^{*, #}	133.74 ± 54.81 ^{*, #, &}	86.496	< 0.001

Note: *indicates compared with the same group before treatment; $P < 0.05$, #indicates compared with the control group at the same time point $P < 0.05$, &indicates compared with subgroup at the same time point $P < 0.05$.

the group was (69.33 + 21.84) ppb and non-EOS asthma was (53.45 + 18.64) ppb. There were statistical differences among the three groups ($P < 0.001$). Post-tests showed that levels of FeNO in EOS and non-EOS asthma groups were higher than those in the control group ($P < 0.001$). EOS asthma levels were higher than those in the non-EOS asthma group ($P < 0.001$). After treatment, levels of FeNO in the control group were (16.83 + 5.99) ppb. EOS asthma was (49.75 + 18.59) ppb and non-EOS asthma was (38.91 + 17.38) ppb. There were significant differences among the three groups ($P < 0.001$). Post-tests showed that levels of FeNO in EOS and non-EOS asthma groups were higher than those in the control group ($P < 0.001$). EOS asthma levels were higher than those in the non-EOS asthma group ($P < 0.001$). According to comparisons, FeNO levels of EOS and non-EOS asthma groups, after treatment, were lower than those before treatment ($P < 0.001$) (**Table 2**).

IgE testing

Before treatment, levels of IgE in the control group were (21.43 + 10.38) IU/mL. EOS asthma was (225.88 + 98.26) IU/mL and non-EOS asthma was (163.14 + 61.25) IU/mL. There were statistical differences among the three groups ($P < 0.001$). Post-tests showed that IgE levels of EOS and non-EOS asthma groups were higher than those of the control group ($P < 0.001$). EOS asthma levels were higher than those of the non-EOS asthma group ($P < 0.001$). After treatment, IgE levels of the control group were (22.18 + 10.42) IU/mL. EOS asthma was (173.34 + 94.17) IU/mL and non-EOS asthma was (133.74 + 54.81) IU/mL. There were statis-

tical differences among the three groups ($P < 0.001$). Post-tests showed that IgE levels of EOS and non-EOS asthma groups were higher than those of the control group ($P < 0.001$). EOS asthma was higher than that of non-EOS asthma ($P < 0.001$). IgE levels of EOS and non-EOS asthma groups, after treatment, were lower than those before treatment ($P < 0.001$) (**Table 3**).

FEV1% testing

Before treatment, the FEV1% of the control group was (91.24 ± 13.88). EOS asthma was (41.75 ± 11.42) and non-EOS asthma was (47.58 ± 12.19). There were statistical differences among the three groups ($P < 0.001$). Post-tests showed that FEV1% of the EOS and non-EOS asthma groups was lower than that of the control group ($P < 0.001$). There were no statistical differences between the EOS asthma and non-EOS asthma groups ($P > 0.05$). After treatment, the FEV1% of the control group was (92.3 ± 13.14). EOS asthma was (83.44 ± 12.75) and non-EOS asthma was (84.31 ± 13.28). There were statistical differences among the three groups ($P < 0.001$). Post-tests showed that the FEV1% of EOS asthma and non-EOS asthma groups was lower than that of the control group ($P < 0.001$). There were no statistical difference between EOS asthma and non-EOS asthma groups ($P > 0.05$). According to comparisons, FEV1% of EOS and non-EOS asthma groups was higher than that before treatment ($P < 0.001$) (**Table 4**).

Correlation analysis

Pearson's results showed that FeNO was positively correlated with expression of IgE

Table 4. FEV1% test

	Control group	EOS asthma	Non-EOS asthma	F value	P value
Before treatment	91.24 ± 13.88	41.75 ± 11.42 [#]	47.58 ± 12.19 [#]	198.647	< 0.001
After treatment	92.33 ± 13.14	83.44 ± 12.75 ^{*,#}	84.31 ± 13.28 ^{*,#}	6.182	0.003

*P<0.05 compared with that before treatment. [#]P<0.05 compared with control group.

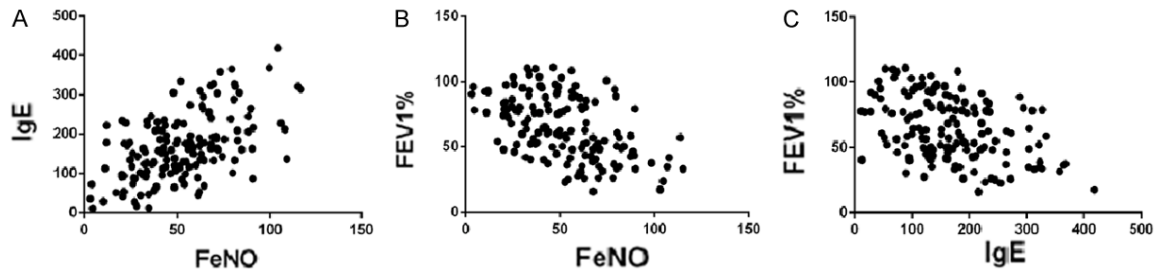


Figure 1. Correlation between FeNO, IgE, and FEV1%. A. Correlation between FeNO and IgE. B. Correlation between FeNO and FEV1%. C. Correlation between IgE and FEV 1%. FeNO was positively correlated with expression of IgE ($r = 0.542$, $P < 0.001$) and negatively correlated with FEV1% ($r = -0.512$, $P < 0.001$). Expression of IgE was negatively correlated with FEV1% ($r = -0.410$, $P < 0.001$).

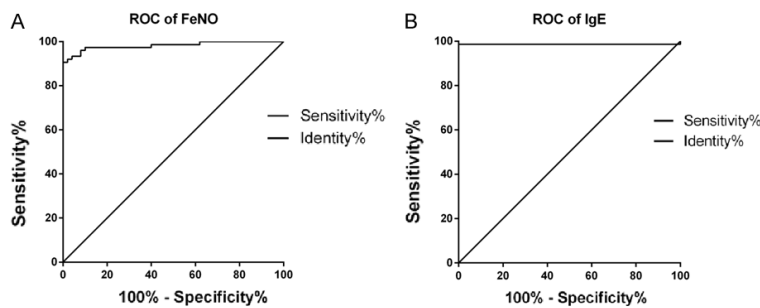


Figure 2. Diagnostic value of FeNO and IgE in children with asthma. A. The diagnostic value of FeNO in children with asthma. B. The diagnostic value of IgE in children with asthma. The area under the curve of FeNO was 0.982 (95% CI 0.962 to 1.003). When FeNO reached 32 ppb, sensitivity was 90.67% and specificity was 100%. The area under the curve of IgE was 0.987 (95% CI 0.961 to 1.013). When IgE reached 25.23 IU/mL, sensitivity was 98.67% and specificity was 100%.

($r = 0.542$, $P < 0.001$) and negatively correlated with FEV 1% ($r = -0.512$, $P < 0.001$). Expression of IgE was negatively correlated with FEV 1% ($r = -0.410$, $P < 0.001$) (**Figure 1**).

Diagnostic value of FeNO and IgE in children with asthma

ROC curves showed that the area under the curve (AUC) of FeNO in the diagnosis of children with asthma was 0.982 (95% CI 0.962 to 1.003). When the optimal cut-off of FeNO was 32 ppb, sensitivity was 90.67% and specificity was 100%. The AUC of IgE in the diagnosis of children with asthma was 0.987 (95% CI 0.961

to 1.013). When the optimal cut-off of IgE was 25.23 IU/mL, sensitivity was 98.67% and specificity was 100% (**Figure 2**).

Diagnostic value of FeNO and IgE in EOS asthma

ROC curves showed that the AUC of FeNO in the diagnosis of EOS asthma was 0.724 (95% CI 0.606 to 0.841). When the optimal cut-off of FeNO was 52.02 ppb, sensitivity was 51.16% and specificity was 87.10%. The AUC of IgE in the diagnosis of EOS asthma

was 0.674 (95% CI 0.538 to 0.809). When the optimal cut-off of IgE was 250.10 IU/mL, sensitivity was 95.45% and specificity was 45.16% (**Figure 3**).

Discussion

Bronchial asthma is a heterogeneous disease of the respiratory system caused by allergens, climate change, mental factors, and genetic factors. However, the pathogenesis has not been fully examined [18, 19]. Due to unstable conditions and pathological changes in the airway, early diagnosis of children with bronchial asthma is of great significance, aiming to avoid irreversible airway damage [20]. De-

Diagnostic value of fractional exhaled nitric oxide and IgE

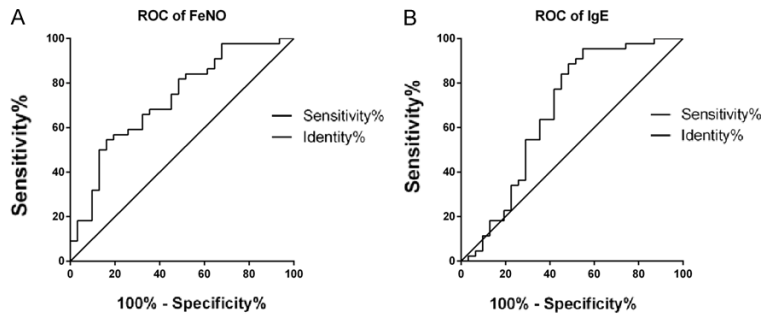


Figure 3. A. Diagnostic value of FeNO in EOS asthma. B. Diagnostic value of IgE in EOS asthma. The area under the curve of FeNO for the diagnosis of EOS asthma was 0.724 (95% CI 0.606 to 0.841). When FeNO reached 52.02 ppb, sensitivity was 51.16% and specificity was 87.10%. The area under the curve of IgE for the diagnosis of EOS asthma was 0.674. (95% CI 0.538 to 0.809), when IgE reached 250.10 IU/mL, sensitivity was 95.45% and specificity was 45.16%.

tection of airway inflammation is an important process in the treatment of asthma. Airway inflammation runs through the whole process of asthma. However, there are no routine methods of detecting airway inflammation in clinic. Detection depends on symptom control and pulmonary function testing of patients [21]. To solve this problem, the current study analyzed the application of FeNO and IgE in the diagnosis of children with asthma. The current study aimed to provide a reference for clinical treatment of asthma and assessment of airway inflammation.

In the 1990s, studies by Alving K [22] showed that levels of FeNO in patients with asthma increased. This attracted the attention of scholars. FeNO levels of patients with asthma were also shown to decrease after hormone therapy [23, 24]. The study also showed that FeNO and IgE levels of children with asthma increased, while FEV1% decreased, compared with healthy controls. FeNO, IgE, and FEV1% were improved after treatment. According to Spearman's analysis, FeNO, IgE, and FEV1% are negatively correlated. FEV1% is one of the important methods of assess the severity of asthma [25]. Studies have revealed that levels of FeNO are associated with the efficacy of asthma treatment, playing a role in prediction. Studies by Fielding [26] showed that monitoring the dynamic changes of FeNO could predict the therapeutic effects of asthma. With every 10% increase in FeNO, the risk of uncontrolled asthma increases by 1.02. FeNO is also an independent factor in evaluating the prognosis of asthma. The American Thoracic Society and

European Respiratory Society have suggested that FeNO can assist in the diagnosis of asthma, assessing the efficacy of asthma and developing criteria for judgement [9, 27]. However, no agreements have been reached concerning specific critical value of FeNO in the diagnosis of asthma and monitoring of the efficacy of asthma. Some studies have shown that the critical value of FeNO in the diagnosis of asthma was 35 ppb. However, those with more than 35 ppb could be diagnosed as asthma. Another study [28] showed that people that suffered from asthma may recur when FeNO reaches 22 ppb, while 49 ppb indicates the relapse of asthma. In the current study, asthma diagnosed by FeNO with a critical value of 32 ppb was in accord with that of previous studies. Moreover, the current study showed that FeNO and IgE have similar efficacy levels in the diagnosis of asthma, improving the credibility of current results. Analysis of diagnostic value of FeNO and IgE in EOS asthma and non-EOS asthma showed that the critical value of FeNO was 52 ppb, while IgE was 250.10 IU/mL. $\text{FeNO} \geq 50$ ppb was the standard from the American Thoracic Society in 2011 [29]. $\text{FeNO} \geq 39$ ppb was the standard from the National Institute for Health and Clinical Excellence in 2014. Results are quite different because of race, age, and immunity levels of the children [30]. Moreover, some studies have suggested that the single test of FeNO was not enough [31].

There were shortcomings to the current study. This study did not measure any variables that reflected inflammation changes, except FeNO. Some studies have found that FeNO levels in different asthma phenotypes can be affected by many internal factors, such as obesity and age [32]. These were not analyzed in the current study. Although the exact cut-off values were provided, present results need to be verified in further studies. Finally, the case source was single, perhaps leading to bias.

In conclusion, levels of FeNO in children with asthma were increased, while FEV1% levels decreased. These levels were negatively corre-

lated, suggesting that FeNO was associated with the diagnosis of children with asthma. FeNO ≥ 32 ppb indicates that children suffered from asthma. When FeNO ≥ 52 , EOS asthma and non-EOS asthma could be diagnosed.

Disclosure of conflict of interest

None.

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