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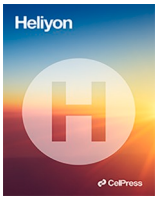

Research article

The change of FeNO is correlated with asthma control and lung function

Yanmin Gao [a,1], Zhenyu Li [b,1], Nengshun Wu [a], Chunxia Jiang [a], Yiran Liu [b], Shenxuan Zhou [b], Anhui Ning [b], Siqi Li [b], Minjie Chu [b,**], Qing Chang [a,*]

[a] Department of Pediatrics, the Eighth People's Hospital of Wuxi, Wuxi, China
[b] Department of Epidemiology, School of Public Health, Nantong University, Nantong, China

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ABSTRACT

Objective: To investigate the changes in fractional exhaled nitric oxide (FeNO) after treatment and the association between FeNO changes and the prognosis and lung function of children with asthma.

Methods: A total of 144 children newly enrolled with non-standardized treatment of asthma were recruited between September 2020 and December 2021. The children were divided into two groups according to the initial FeNO (0 day), and the changes in FeNO after Budesonide/Formoterol Inhalation Powder Mist (B/FIPM) treatment were observed in different subgroups in correlation with future outcomes after 1 year (well controlled or partly controlled) and lung function.

Results: The study showed that B/FIPM therapy significantly reduced FeNO levels and eosinophils (EOS) counts, improving pulmonary function ($P < 0.01$). FeNO levels significantly decreased in the well controlled group after 1 week treatment but not after 2 weeks. The partly controlled group showed sustained benefits after 2 weeks treatment ($P < 0.01$). Besides, among the patients with initial FeNO $\leq$35 ppb, the proportion of well controlled outcome was significantly higher in the group of ΔFeNO >0 (72.73 %) than that in the ΔFeNO ≤ 0 group (53.85 %) ($P = 0.042$).

Conclusion: B/FIPM is effective in reducing FeNO levels and EOS counts and restoring lung function in children with asthma. In addition, post-treatment changes in FeNO were predictive of prognosis and correlated with post-treatment lung function.

1. Introduction

Asthma, a chronic respiratory disease affecting all age groups, is characterized by periodic and reversible wheezing, chest tightness, breathlessness, and coughing [1]. Its heterogeneous nature and variable symptoms complicate both diagnosis and treatment [2]. Affecting over 350 million people globally, asthma's rising incidence poses a significant public health challenge [3]. Accurate diagnosis and effective anti-inflammatory treatment are essential in managing this condition [4].

Given the complexity of asthma, its classification by severity is crucial for guiding treatment and assessing prognosis. Asthma is

* Corresponding author.
** Corresponding author.
E-mail addresses: chuminjie@ntu.edu.cn (M. Chu), q_chang@sohu.com (Q. Chang).
[1] These authors contributed equally to this work.

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subdivided into different severity levels, each of which uniquely impacts lung function and long-term outcomes [5]. The clinical manifestations, disease progression, and treatment responses vary significantly across these levels, highlighting the importance of tailored management strategies [6]. Furthermore, asthma presents differently between adults and children, with notable differences in both severity and response to treatment. Understanding these distinctions is essential for optimizing care and improving patient outcomes.

Asthma is the most prevalent chronic childhood disease, with increasing cases in recent years [7]. Compared to adults, children with severe asthma exhibit higher eosinophil (EOS) counts, greater allergen sensitivities, and elevated IgE levels [8]. Despite treatment with inhaled glucocorticoids and bronchodilators, nearly half of these cases remain uncontrolled [9]. This underscores the urgent need for effective diagnostic markers and optimized treatment strategies.

While most children with asthma achieve control through pharmacotherapies, a significant number of children continue to experience exacerbations, leading to frequent hospital admission in developed countries [10]. This underscores the need for better screening and treatment options to mitigate asthma's impact on children's health. Current understanding of asthma pathogenesis highlights the central role of airway inflammation, particularly in the type 2 (T2) immune response [11]. Among T2 biomarkers, fractional exhaled nitric oxide (FeNO) has emerged as a key indicator of allergic airway inflammation, showing the strongest correlation with asthma exacerbations compared to other markers [12,13]. FeNO is not only a reliable marker for monitoring airways inflammation but also a practical tool in guiding asthma treatment due to its non-invasive, safe and cost effective nature [14,15]. Therefore, we selected FeNO as the focus of our study to minimize risk to children while effectively assessing asthma control.

Global INitiative for Asthma (GINA) lists raised FeNO as a risk factor for future asthma attacks, while National Institute Of Clinical Examiners (NICE) recommends consideration of FeNO measurements for managing symptomatic asthma despite inhaled corticosteroids [16]. Effective asthma management requires regular assessment of control, yet guidelines offer limited practical advice for monitoring in children [17]. Thus, using FeNO to evaluate changes in treatment, particularly the effectiveness of corticosteroids, is crucial. The American Thoracic Society (ATS) has conditionally recommended FeNO testing since 2021 to help reduce exacerbations when adjusting asthma treatment [18,19]. Budesonide/Formoterol Inhalation Powder Mist (B/FIPM) is known to reduce airway inflammation and hyperresponsiveness, but further research is needed to optimize dosing and minimize harm in pediatric patients, ensuring maximum therapeutic benefit with minimal risk.

This study aimed to investigate whether changes in FeNO levels under B/FIPM treatment could predict long-term outcomes and lung function in children with asthma. We began by comparing FeNO levels and lung function before and after B/FIPM treatment to assess its efficacy. Next, we analyzed FeNO changes over time across different outcome scenarios. Finally, we examined the correlation between FeNO changes and future outcomes, considering whether a continuous change index could predict outcomes in new patients.

2. Methods

2.1. Study design and study population

Between September 2020 and December 2021, we enrolled 144 children, aged 4–14 years, diagnosed with asthma at the department of pediatrics, the Eighth People's Hospital of Wuxi, Wuxi, China. These participants had not undergone standardized treatment previously and their asthma diagnoses aligned with the criteria outlined in the 2016 edition of the *Guidelines for the Diagnosis and Management of Bronchial Asthma in Children* [20]. We gathered basic data including age, gender, height, weight, and histories of food and family allergies. To ensure the study's integrity, we excluded children with underlying conditions such as inherited metabolic disorders and congenital heart diseases. At their initial visit, we measured their initial FeNO (0 day) and lung function. Treatment with B/FIPM (80/4.5ug, 60 puffs/strike, manufactured by AstraZeneca, Sweden, Import Registration No. H20140459) commenced thereafter. In the first month, weekly treatments were administered for the initial two weeks, with FeNO values recorded after the first and second weeks. Follow-ups were conducted at the end of the first month and subsequently every three months to assess FeNO and lung function. After one year, the 144 children were categorized into either the well controlled group or the partly controlled group, based on their final treatment outcomes (Fig. 1). The above records and the medical condition assessment were all completed by the attending physician. Informed consent was obtained from all subjects involved in the study. The study was reviewed and approved by the ethics committee of the Eighth People's Hospital of Wuxi (202001F001).

2.2. Definition

We combined the classification criteria of ATS and the European Respiratory Society (ERS) clinical guidelines, and we categorized children with asthma into two groups based on initial FeNO $\leq$35 ppb and FeNO $>$35 ppb. Patients categorized in the well controlled group had fully recovered, whereas the partly controlled group included partially cured or not cured at all. Well controlled asthma was

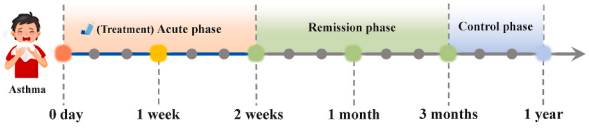

Fig. 1. Timeline of post-diagnostic treatment for children with asthma.

defined as the absence of daytime coughing or wheezing, no nighttime wheezing, no need for emergency asthma relief medication, and no activity limitation due to wheezing or coughing. Partly controlled asthma was defined as the presence of 1–2 of the aforementioned criteria. Pulmonary function tests are important tools for diagnosing asthma and assessing its severity and level of control. In our study, we collected a number of pulmonary function parameters including forced lung volume (FVC), peak expiratory flow rate (PEF), forced expiratory volume in 1 s (FEV_1), FEV_1/FVC ratio, as well as 50 % forced expiratory flow rate (FEF_{50}), 75 % forced expiratory flow rate (FEF_{75}), and maximal mid-expiratory flow rate (MMEF).

2.3. Methods for measuring lung function parameters

The spirometry equipment we used is the Master Screen model from Jäger (Germany). All lung function parameters are expressed as the ratio of the measured value to the predicted value for each child. The measured values were obtained at the spirometry equipment. The predicted values were determined using the Zapletal equation, which is widely used in clinical diagnostics. This equation is based on a large global dataset, including both Asian populations and Caucasian data adjusted with ethnic correction factors. This ensures the applicability and accuracy of the predicted values across diverse patient groups.

2.4. Treatment modalities

The treatment regimen included B/FIPM (80/4.5 μg) administered as maintenance therapy with twice-daily inhalation. For children experiencing acute exacerbations, additional treatment included loratadine or montelukast sodium for 1–2 weeks, or short-term salbutamol nebulized inhalation for 3–7 days, depending on the severity of symptoms.

2.5. Statistical analysis

Continuous variables are expressed as mean ± standard deviation. To ensure comparability of baseline information, we used independent sample *t*-test and Mann-Whitney *U* test for analyzing differences between two groups for continuous variables and the chi-square test for comparing categorical variables between groups. Paired *t*-tests were employed to assess changes in FeNO levels and lung function indicators before and after treatment. The rate of change in FeNO levels was calculated by comparing continuous FeNO measurements at different time points and considering the mean values. In addition, Pearson correlation analysis was conducted to examine the relationships and strengths of associations between FeNO levels and lung function indicators. *P*-value less than 0.05 indicated statistical significance. We used R 4.3.1 for data analysis and statistics.

Table 1
Basic information of the study subjects.

Variables	Well controlled group (N = 96)	Partly controlled group (N = 48)	t/ χ^2	*P*
Gender (Male/Female)	64/32	29/19	0.546	0.460
Age (years)	6.48 ± 1.98	6.21 ± 1.91	−0.783	0.435
Height (cm)	121.58 ± 12.36	120.38 ± 13.55	−0.529	0.598
Weight (kg)	24.82 ± 8.42	25.73 ± 10.27	0.527	0.599
Dermatitis (Yes/No)	24/72	17/31	1.705	0.192
Rhinitis (Yes/No)	80/16	40/8	0.000	1.000
EOS ($\times 10^9$/L)	0.36 ± 0.26	0.36 ± 0.25	0.025	0.980
EOS%	4.23 ± 2.99	3.98 ± 2.42	−0.532	0.596
FeNO (ppb)	28.76 ± 24.88	25.90 ± 20.19	−0.692	0.490
FVC (%)	90.89 ± 13.52	89.23 ± 12.94	−0.705	0.482
PEF (%)	79.60 ± 15.60	78.85 ± 17.73	−0.257	0.798
FEV_1 (%)	91.95 ± 13.74	90.89 ± 14.36	−0.427	0.670
FEV_1/FVC (%)	96.06 ± 13.57	100.53 ± 7.89	2.483	<0.05
FEF_{50} (%)	70.57 ± 17.64	72.48 ± 18.62	0.600	0.550
FEF_{75} (%)	66.10 ± 20.20	75.27 ± 26.36	2.306	<0.05
MMEF (%)	69.38 ± 18.49	72.77 ± 19.99	1.005	0.317

EOS: eosinophils; FeNO: exhaled nitric oxide; FVC: forced vital capacity; PEF: Peak expiratory flow FEV_1: forced expiratory volume in 1 s; FEV_1/FVC: Rate of 1 s; FEF_{50}:50 % forced expiratory flow; FEF_{75}:75 % forced expiratory flow; MMEF: Maximal mid-expiratory flow; Well controlled group: asthma symptoms disappeared; Partly controlled group: The symptoms were partially relieved but not completely cured.
t: Independent sample *t*-test. χ^2: Chi-square test.
The mean values of lung function parameters in the table are calculated as the ratio of the measured value of the parameter to the predicted value for each child, with the predicted values determined using the Zapletal equation.

3. Results

3.1. Basic information of the respondents

In this study, we studied 144 children with asthma, including 93 boys and 51 girls. These subjects were then categorized into two groups based on their post-treatment control status: the well controlled group, consisting of 96 children, and the partly controlled group, comprising 48 children. We conducted a statistical analysis of the baseline data of the study participants. The analysis revealed no statistically significant differences in clinical data such as gender, age, height, and weight between the two groups ($P > 0.05$), indicating that the groups were comparable (Table 1).

3.2. Assessing the impact of B/FIPM treatment on FeNO levels and pulmonary function in asthmatic children

To evaluate the overall effectiveness of B/FIPM treatment in children with asthma, we compared FeNO levels and other lung function indices between the initial diagnosis period (0 day) and remission phase (3 months remission). Our findings demonstrated a significant reduction in FeNO and EOS levels and notable improvements in lung function following treatment, all of which were statistically significant ($P < 0.01$). These results are presented in Table 2.

3.3. Comparative analysis of FeNO level changes in well controlled group and in partly controlled group

To delve deeper into the differences in treatment outcomes between the well controlled group and the partly controlled group, we conducted separate analyses for each group at various stages: the difference from the acute stage (0 day) to treatment at 1 week, from 1 week to 2 weeks of treatment, from 2 weeks of treatment to 1 month of remission, and from 1 month to 3 months of remission. In the well controlled group, the change from the acute stage (0 day) to 1 week of treatment showed a statistically significant difference ($\Delta FeNO = 8.90 \pm 17.22$, $P < 0.01$). However, the difference between the treatment 1 week and treatment 2 weeks was not statistically significant ($\Delta FeNO = 0.56 \pm 11.66$, $P = 0.637$). Conversely, in the partly controlled group, significant differences were observed both from the acute stage (0 day) to 1 week of treatment ($\Delta FeNO = 6.19 \pm 18.70$, $P < 0.05$) and from 1 week to 2 weeks of treatment ($\Delta FeNO = 3.94 \pm 9.30$, $P < 0.01$) (Table 3). The above results showed that the decrease in FeNO after the 1 week of treatment was more significant in both the well controlled and partly controlled groups, but the decrease in the well controlled group was more pronounced than that in the partly controlled group. These suggest that a significant therapeutic effect was achieved in the well controlled group immediately after just 1 week of treatment.

3.4. Analyzing FeNO changes to predict future prognostic outcomes

The above findings revealed notable differences across three specific time points: the acute phase (0 day), after 1 week of treatment, and after 2 weeks of treatment. To investigate these differences further, we categorized patients into two groups based on their FeNO levels during the acute phase (0 day): those with levels $\leq$35 ppb and those with levels >35 ppb. We then examined the changes in FeNO levels from the acute phase (0 day) to after 1 week of treatment, and from 1 week to 2 weeks of treatment, within both the well controlled group and the partly controlled group. The results showed that in the FeNO $\leq$35 ppb group, the mean difference in FeNO after 1 week of treatment was statistically significantly higher in the well controlled group than in the partly controlled group ($P < 0.05$). Conversely, the mean difference after 2 weeks of treatment was significantly higher in the partly controlled group than in the well controlled group ($P < 0.05$). However, these differences were not statistically significant in the group of FeNO >35 ppb ($P > 0.05$). These results are illustrated in Fig. 2.

Table 2
Comparison of pulmonary function related indexes before and after treatment.

Variables	Before treatment (0 day)	After treatment (3 months remission)	*P*
FeNO (ppb)	27.92 ± 23.58	17.01 ± 12.13	<0.01
EOS ($\times 10^9$/L)	0.36 ± 0.25	0.25 ± 0.20	<0.01
EOS%	4.15 ± 2.81	3.04 ± 2.31	<0.01
FVC (%)	90.19 ± 13.24	98.06 ± 11.57	<0.01
PEF (%)	79.22 ± 16.28	95.84 ± 15.65	<0.01
FEV_1 (%)	91.47 ± 13.88	104.69 ± 12.27	<0.01
FEV_1/FVC (%)	97.54 ± 12.17	105.37 ± 7.13	<0.01
FEF_{50} (%)	71.19 ± 17.99	92.84 ± 16.93	<0.01
FEF_{75} (%)	69.18 ± 22.86	90.52 ± 21.77	<0.01
MMEF (%)	70.49 ± 19.07	93.35 ± 17.52	<0.01

The mean values of lung function parameters in the table are calculated as the ratio of the measured value of the parameter to the predicted value for each child, with the predicted values determined using the Zapletal equation.

Table 3
ΔFeNO between different time points.

Group	Previous FeNO(ppb)	Posterior FeNO(ppb)	ΔFeNO[a](ppb)	*P*
Well controlled group				
ΔFeNO (0 day −1 week)	28.76 ± 24.88	19.86 ± 15.38	8.90 ± 17.22	<0.01
ΔFeNO (1 week - 2 weeks)	19.86 ± 15.38	19.30 ± 17.66	0.56 ± 11.66	0.637
ΔFeNO (2 weeks −1 month)	19.30 ± 17.66	18.44 ± 14.56	0.87 ± 10.73	0.432
ΔFeNO (1 month - 3 months)	18.44 ± 14.56	17.93 ± 13.50	0.51 ± 8.77	0.570
Partly controlled group				
ΔFeNO (0 day −1 week)	25.90 ± 20.19	19.71 ± 13.17	6.19 ± 18.70	<0.05
ΔFeNO (1 week - 2 weeks)	19.71 ± 13.17	15.77 ± 10.00	3.94 ± 9.30	<0.01
ΔFeNO (2 weeks −1 month)	15.77 ± 10.00	16.25 ± 8.83	−0.48 ± 5.12	0.520
ΔFeNO (1 month - 3 months)	16.25 ± 8.83	15.25 ± 9.00	1.00 ± 7.48	0.359

[a] The mean of the previous FeNO minus the Posterior FeNO.

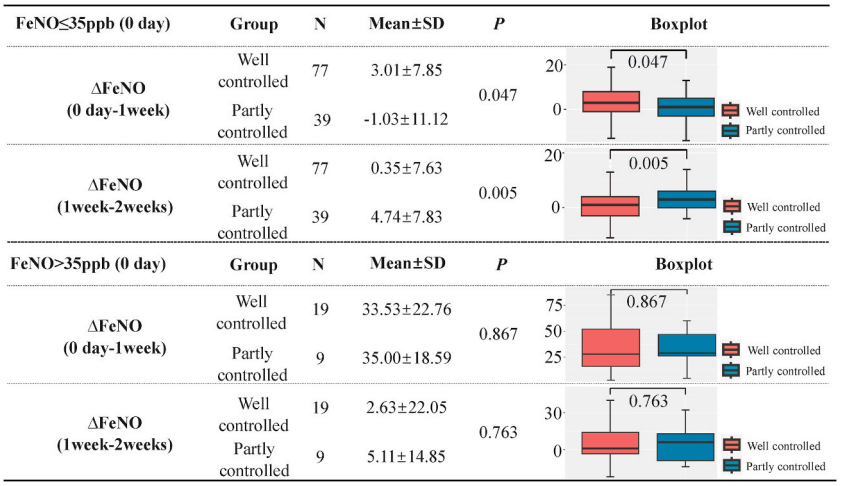

Fig. 2. Analysis of treatment differences between groups under the subgroups FeNO ≤35 ppb and >35 ppb.
*ΔFeNO (0 day - 1 week), ΔFeNO (1 week - 2 weeks): the mean of the previous FeNO minus the Posterior FeNO.
(**Note:** FeNO: fractional exhaled nitric oxide).

3.5. Analysis of the relationship between the rise and fall of FeNO after treatment at different FeNO levels

To further understand the efficacy of treatment from initial diagnosis (0 day) to 1-week post-treatment in patients, we stratified them based on their initial FeNO levels (0 day) into two groups: FeNO ≤35 ppb and FeNO >35 ppb. This stratification was employed to observe asthma control post-treatment in different groups. Our study results show that within the group with FeNO levels ≤35 ppb, there was a significant difference in the final outcomes between individuals who experienced a decrease in FeNO levels post-treatment (ΔFeNO >0) and those who experienced an increase (ΔFeNO ≤0) ($\chi^2 = 4.135$, $P = 0.042$). Specifically, the proportion of well controlled patients in the ΔFeNO >0 (72.73 %) group was significantly higher than that in the ΔFeNO ≤0 group (53.85 %). (Table 4).

3.6. Correlation between FeNO and peripheral blood EOS during the acute phase (0 days) of pediatric asthma

The study revealed discernible variations in FeNO levels among children across different groups and time points. We delved deeper

Table 4
Analysis of the 1-week treatment difference and outcome.

Group	ΔFeNO[a] (0 day −1 week)	Well controlled	Partly controlled	χ^2	*P*
FeNO≤35 ppb (0 day)	≤0(N = 39)	21(53.85 %)	18(46.15 %)	4.135	0.042
	>0(N = 77)	56(72.73 %)	21(27.27 %)		
FeNO>35 ppb (0 day)	≤0(N = 0)	–	–	–	–
	>0(N = 28)	19(67.86 %)	9(32.14 %)		

χ^2: Chi-square test.
[a] The mean of the previous FeNO minus the Posterior FeNO.

to examine the correlation between acute phase FeNO (0 day) and lung function, closely observing how changes in FeNO levels influenced lung function indices. The results indicated a significant correlation between acute phase FeNO (0 day) levels and both absolute EOS counts ($R = 0.31$, $P < 0.01$) and EOS% ($R = 0.38$, $P < 0.01$), with all results demonstrating statistical significance. These findings are comprehensively illustrated in Fig. 3.

3.7. Analysis of pulmonary function results in acute and remission phases (3 months)

The study's findings revealed a statistically significant difference between the well controlled and partly controlled groups in both the ≤35 ppb and >35 ppb FeNO categories throughout the treatment period. To further elucidate this disparity, we explored the association between the variation in FeNO levels from the initial diagnosis period (0 day) to the first week of treatment, and lung function during the subsequent remission phase (3 months). The aim was to determine whether treatment effects could serve as predictors for lung function outcomes. A significant correlation between changes in treated FeNO levels and lung function in remission was observed only in the ≤35 ppb group ($P < 0.05$). However, this correlation was not apparent in the >35 ppb group, as depicted in Fig. 4.

4. Discussion

Based on the above studies, B/FIPM significantly reduces FeNO and EOS levels, enhancing lung function. After 1 week of treatment, the well controlled group showed a more significant decrease in FeNO levels than the partly controlled group, especially notable in patients with initial FeNO ≤35 ppb. Contrarily, after 2 weeks of treatment, the partly controlled group exhibited a greater reduction in FeNO levels compared to the well controlled group, indicating differing response dynamics over time.

FeNO was first demonstrated to be elevated in patients with asthma in the early 1990s, and interest in its potential role in the diagnosis and management of asthma has been intense. Interest in FeNO is based on the hypothesis that FeNO is a marker of asthma and asthma control that reflects eosinophilic airway inflammation [21]. At the same time, some studies have pointed out that FeNO cannot be used as a marker of acute exacerbation [22], but only as an indicator of auxiliary diagnosis. More scholars have proposed that FeNO should be continuously observed to reflect individual changes in airway inflammation and that the level of change in FeNO is more instructive for asthma treatment. In this paper, FeNO was monitored continuously across 5 stages, revealing that the well controlled group showed a significant reduction in FeNO levels after 1 week of treatment compared to initial diagnosis. The critical role of B/FIPM in achieving control is evident, as the subsequent reduction in FeNO after the second week was minimal. In contrast, the partly controlled group exhibited a gradual reduction in FeNO over both the first and second weeks, reflecting the incomplete control achieved in these patients.

Currently, there is limited economic evaluation of FeNO measurement. However, research by Berg and colleagues has demonstrated that incorporating FeNO in the diagnosis and management of asthma in Germany is more cost-effective compared to standard guideline-based management. This cost-effectiveness is primarily attributed to the reduction in exacerbations and hospitalizations, resulting from improved disease control, particularly in mild to severe adult patients [23]. Additionally, studies have indicated that children with asthma often exhibit lower adherence to medication, a trend that may correlate with age and elevated FeNO levels. Therefore, it is crucial to intensify efforts to enhance adherence to asthma controller medications, especially in patients receiving inhaled therapy who exhibit elevated FeNO levels [24]. B/FIPM, the therapeutic agent used in this study, has high patient acceptance and can be effective in improving compliance and thereby enhancing the cure rate in children.

This study aims to explore the relationship between FeNO level variations and asthma outcomes in children [25]. It investigates the

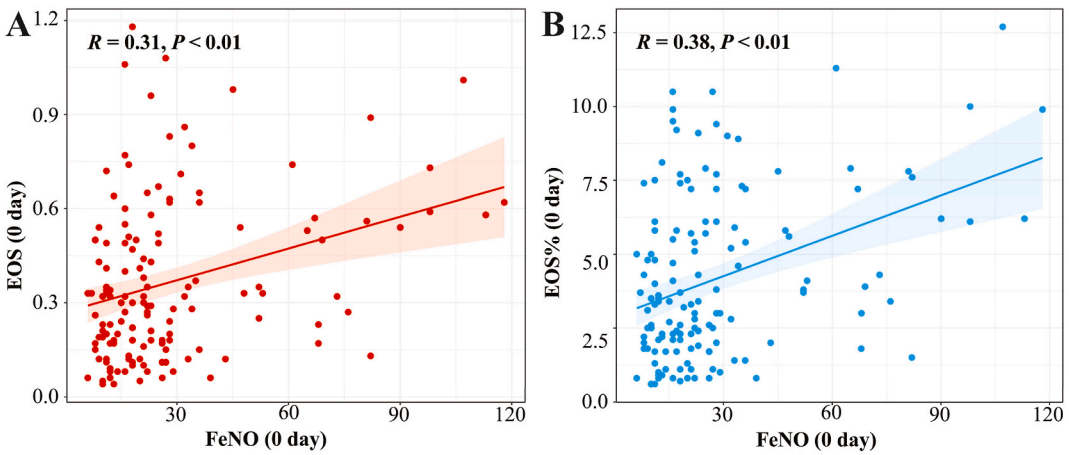

Fig. 3. Analysis of the correlation between acute phase FeNO (0 day) and acute phase lung function (0 day). (A) Acute phase FeNO (0 day) correlates with acute phase EOS (0 day). (B) Acute phase FeNO (0 day) and acute phase EOS % (0 day) correlation. (**Note:** FeNO: fractional exhaled nitric oxide; EOS: eosinophils).

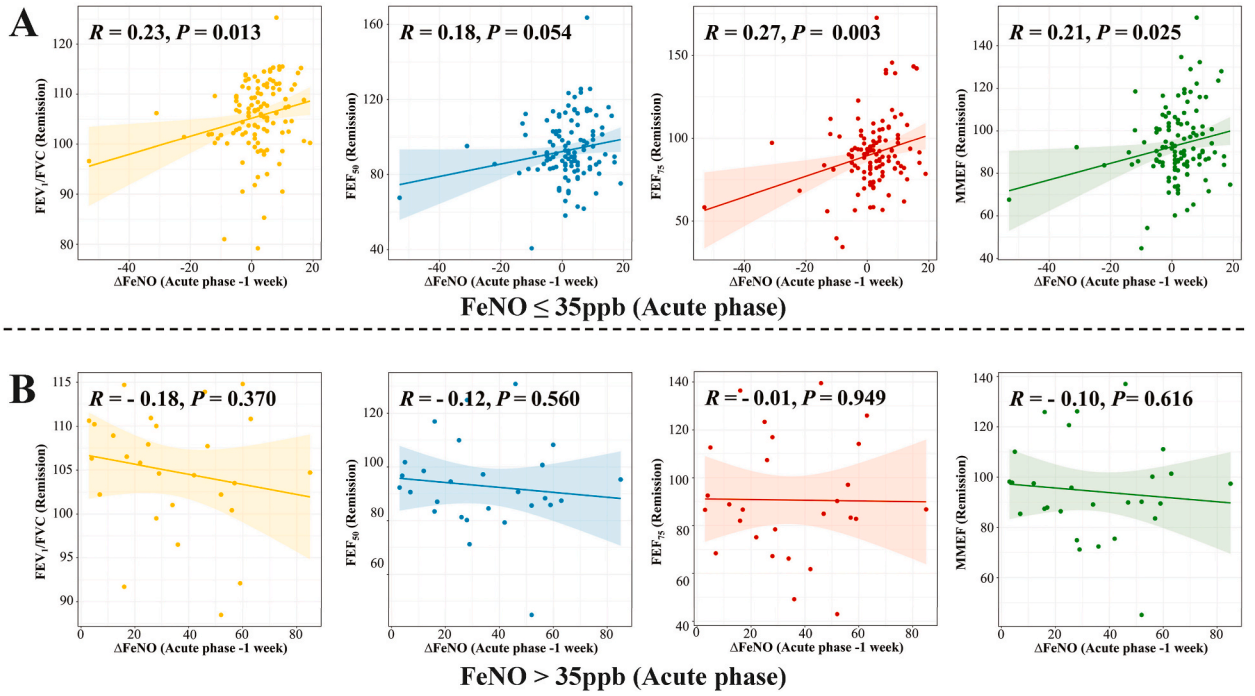

Fig. 4. Correlation analysis of ΔFeNO (0 day-1 week) with lung function in remission at FeNO ≤35 ppb and >35 ppb. (A) Correlation between ΔFeNO (0 day-1 week) and lung function in remission at FeNO ≤35 ppb. (B) Correlation between ΔFeNO (0 day −1 week) and lung function in remission at FeNO >35 ppb.
*ΔFeNO (0 day (Acute phase) - 1 week): the mean of the previous FeNO minus the Posterior FeNO.
(**Note:** FeNO: fractional exhaled nitric oxide).

correlation between asthma control and lung function through individual changes in FeNO values. Additionally, the study assesses varied responses to B/FIPM treatment, recognizing FeNO as an indicator of type-2 inflammation in airways [26]. Results indicate a significant reduction in FeNO values post-treatment in the well controlled group, with a lesser decline in the partly controlled group. This suggests a potential link between substantial FeNO value changes post-treatment and complete asthma control. However, small changes in FeNO values may be indicative of partially controlled or uncontrolled asthma. The study acknowledges possible biases due to individual variations in drug resistance and health, underscoring the need for further, more comprehensive research in this area.

Pulmonary Function Testing (PFT) plays a crucial role in the diagnosis and management of asthma, with spirometry being the preferred method for assessing lung function. Key pulmonary function metrics such as FEV_1, FVC, and their ratio (FEV_1/FVC) provide objective and quantitative measures of lung physiology [27]. Diverse studies on pulmonary function tests have identified different indices as being more effective in assessing asthma severity. For instance, research by Quanjer et al. [28] indicated that FEV_1, FVC, and the FEV_1/FVC ratio are more effective than Forced Expiratory Flow at 25–75 % ($FEF_{25–75}$) in this regard. Conversely, Lukic and Coates [29] found the FEV_1/FVC ratio to be a superior marker for evaluating asthma severity, while Ratageri et al. [30] suggested that $FEF_{25–75}$ is a better index for severity assessment. Despite numerous efforts to pinpoint the most accurate PFT index for determining asthma severity, the debate remains ongoing. In our study, we found a positive correlation between the post-treatment FeNO changes and remission lung function indices, including FEV_1/FVC, FEF_{50}, FEF_{75}, and MMEF, contributing to this ongoing debate.

FeNO, recognized as a noninvasive marker of inflammation, has predominantly been utilized in research as a potential diagnostic tool for asthma. The innovative aspect of this study lies in its approach to continuously monitor FeNO levels to track the eventual outcomes in children with asthma. We have further refined our analysis by categorizing FeNO levels into ≤35 ppb and >35 ppb, enabling a more detailed examination of the changes in these levels, their implications for future prognosis, and lung function during remission periods. An added advantage of the FeNO test is its affordability and the relative simplicity of its operation and interpretation compared to traditional lung function tests. This simplicity makes it particularly suitable for primary healthcare settings, especially in facilities where pulmonary function testing is not available. FeNO testing can serve as an early indicator of impending asthma attacks, aiding physicians in timely identification and intervention. Its non-invasive nature also makes it more acceptable to children. Therefore, conducting further research to elucidate the clinical significance of FeNO could greatly enhance the precision and long-term management of allergic diseases, such as pediatric asthma.

In the present study, we found that ΔFeNO (0 day-1 week) in the FeNO ≤35 ppb group was positively correlated with several lung function indices, suggesting that the change in FeNO after B/FIPM treatment in these children could, to some extent, be a response to a better improvement in lung function and portend a better prognosis. The FeNO >35 ppb group did not show such a correlation, suggesting that even though this group of children was sensitive to B/FIPM and had rapid relief of symptoms in the acute phase, this is

not a reliable way to judge long-term lung function outcomes. There may be more confounding factors associated with this group of children, and perhaps the mechanisms of inflammatory expression are more complex.

This study offers a novel perspective by focusing on a specific subset of asthmatic patients often overlooked in clinical monitoring, those with FeNO levels ≤35 ppb at initial diagnosis. It emphasizes the importance of monitoring FeNO and lung function changes in these patients' post-medication, using these metrics to predict future health outcomes. This approach not only highlights a neglected group of patients but also suggests a more comprehensive treatment strategy that could significantly improve their prognosis. By incorporating these insights into clinical practice, we can enhance the precision of asthma management and deliver more personalized care.

This study has a few limitations. First, the study realized in the period of COVID-19 pandemic in China, although the study took place during a relatively stable phase of the pandemic, that could not be the accurate moment to include the study subjects due to the strict isolation of COVID-19 in China. Second, the sample size was limited to 144 children, which may restrict the generalizability of the findings, further studies should include more asthmatic children for analyzing more the role of FeNO in the control of asthma in long-term.

5. Conclusion

This study demonstrated that B/FIPM treatment effectively reduces FeNO and EOS levels while improving lung function in children with asthma. Notably, in the FeNO ≤35pbb group, changes in FeNO levels were significantly correlated with lung function during the remission period and the prognosis of the asthma children. These findings suggest that monitoring FeNO changes could serve as a valuable predictor of long-term outcomes in asthma management with B/FIPM, providing a critical tool for optimizing treatment strategies and improving patient prognosis.

Data availability statement

The data supporting this study are not currently available in publicly accessible repositories. Data are available upon reasonable request.

Ethics statement

The study was reviewed and approved by the ethics committee of the Eighth People's Hospital of Wuxi (202001F001).

CRediT authorship contribution statement

Yanmin Gao: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Zhenyu Li:** Writing – original draft, Resources, Investigation, Conceptualization. **Nengshun Wu:** Writing – review & editing, Software, Formal analysis. **Chunxia Jiang:** Writing – original draft, Conceptualization. **Yiran Liu:** Investigation, Data curation. **Shenxuan Zhou:** Software, Formal analysis. **Anhui Ning:** Investigation, Data curation. **Siqi Li:** Investigation, Formal analysis, Data curation. **Minjie Chu:** Visualization, Validation, Supervision, Methodology, Investigation, Funding acquisition. **Qing Chang:** Visualization, Resources, Methodology, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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