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Fractional exhaled nitric oxide and forced expiratory volume in 1 second/ forced vital capacity have predictive value of asthma exacerbation in Korean school children

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Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

Background: The incidence of asthma exacerbation (AE) and the predictive value of spirometry and fractional exhaled nitric oxide (FeNO) in school children have not been evaluated.
Objective: We sought to evaluate the efficacy of spirometry measurement and FeNO monitoring for predicting AE in school children in the Cheongju area in Korea.
Methods: With parental agreement, we studied 170 students aged 7–12 years. Children were evaluated by an asthma specialist using baseline spirometry, skin prick test, seasonal FeNO measurement, and asthma control test. The study participants underwent a physical examination and their medical history was also evaluated by the specialist. They were assessed for asthma control status during regular doctor visits for 1 year.
Results: In total, 160 children (94.1%) completed follow-up and FeNO monitoring. Of which, 26 children (16.3%) had AE. AE was associated with male children and children with allergic rhinitis ($p < 0.05$). While, children with AE tended to have higher FeNO than those without AE, no significant difference was found. The maximum value of FeNO ≥35 ppb was associated with AE ($p < 0.05$). Children with AE had a significantly decreased baseline forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC), %predicted, forced expiratory flow at 25%–75% of FVC ($FEF_{25\%–75\%}$). $FEV_1/FVC < 80\%$ was associated with AE in children regardless of inhalant allergen sensitization (all $p < 0.05$).
Conclusion: Baseline spirometry had a predictive value of AE in school children. Sensitive spirometric parameters such as FEV_1/FVC and $FEF_{25\%–75\%}$ can be used as prognostic factors to predict future childhood AE. FeNO value ≥ 35 ppb during monitoring was associated with AE in school children.

Keywords: Asthma; Exacerbation; Child; Exhaled nitric oxide; Spirometry

INTRODUCTION

Asthma is one of the most common chronic diseases with the highest prevalence (9.9%) in school-aged children (5–14 years) [1]. Childhood asthma is the most common cause of school absences, and 57.9% of asthmatic children have experienced asthma exacerbation (AE) more than once a year [2, 3]. Despite the high prevalence and socioeconomic burden of childhood asthma, diagnosing childhood asthma remains challenging since it is difficult to distinguish it from recurrent wheeze or bronchiolitis in the early stages [3]. Further, asthma is more likely to be overlooked in younger children. Although childhood asthma can resolve spontaneously, some adolescents experience acute initial symptoms despite no previous history of asthma.

Since diagnosis and management of childhood asthma are difficult, several developed countries have an asthma-friendly school program (AFSP) [4]. AFSP screens for asthma and allergic diseases based on the International Study of Asthma and Allergies in Childhood (ISAAC) survey for school-aged children [4, 5]. Several studies conducted in AFSP measured the burden of childhood asthma and the prevalence of asthma in many schools was found to be 4.0%–6.7% [6]. However, the annual incidence of AE in school-aged children is still unknown.

The amount of air one can forcefully exhale in 1 second, or forced expiratory volume (FEV_1), is an independent predictor of AE and considered important in defining asthma severity [7]. The National Asthma Education and Prevention Program guidelines suggest regular spirometry for children with asthma who are ≥5 years of age [8].

FeNO is a noninvasive biomarker for eosinophilic airway inflammation [7] because FeNO can be easily performed independent of forced respiration and is particularly useful in diagnosis of asthma in children [8]. The National Institute for Health and Care Excellence and the British Thoracic Society guidelines recommend the use of FeNO as a tool for diagnosing asthma in children [9]. However, studies have not yet examined its predictive value on asthma prognosis in asthmatic children [7, 10].

The goal of this study was to determine the real impact of asthma in schoolchildren from Cheongju area of South Korea, such as AE and asthma-related school absences through prospective monitoring in order to get information for developing a proper asthma school management. The secondary aim of this prospective study was to identify the predictive ability of spirometry measurement and FeNO monitoring for acute exacerbation of loss of asthma control in elementary schools.

MATERIALS AND METHODS

Study design
This prospective study was performed to identify the predictive value of spirometry measurement and FeNO monitoring for AE including asthma attack. A total of 170 elementary school students in the Cheongju area were enrolled in our study. The participants and their families understood the objectives of this study and provided informed consent. Initially, participants were asked to answer the ISAAC core questionnaire, the presence of early childhood wheezing episodes, and the existence of a current diagnosis of asthma, including any current treatment modality [11]. The questionnaire defined recurrent wheezing

as a lifetime wheeze of more than 3 episodes. Recurrent wheeze must have at least one physician-diagnosed wheeze. Diagnosed asthma was defined as physician-diagnosed asthma.

Trained specialists performed baseline spirometry, skin prick test for common aeroallergens and child allergy specialists performed a routine physical examination and clinical assessment for allergic disease. Study participants prospectively had a regular check-up for asthma control status and history of exacerbation and performed the seasonal FeNO measurement every 3 months. Patients were allowed to receive asthma management from their own physicians. When a participant had AE on regular check-up, we offered prompt in school management for AE and referred the student to his/her primary physician. The Ethics Committee of Chungbuk National University Hospital Institutional Review Board approved the study (2011-09-062) and written informed consent was obtained from the parents of all subjects.

Measurements

Fractional exhaled nitric oxide
FeNO was measured by chemiluminescence using an online nitric oxide monitor (NIOX MINO; Aerocrine AB, Solna, Sweden), according to the European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines [11] and expressed as parts per billion (ppb). The children were instructed to avoid eating, drinking, and to perform any strenuous exercise 2 hours before the FeNO measurements. After inhaling ambient air to total lung capacity through a nitric oxide scrubber, the participants exhaled against expiratory resistance, excluding nasal air. Exhalation times were 10 seconds with a 2-minute analysis period. Repeated exhalations (2 values that agree within 5%, or 3 that agree within 10%) were performed without a nose clip at a constant flow rate of 50 mL/sec.

Pulmonary function testing
Lung function tests were performed with a spirometer (Vmax SensorMedics, Yorba Linda, CA, USA) in accordance with ATS/ERS recommendations [12, 13]. The following variables were obtained from the best of 3 reproducible FVC, FEV_1, forced expiratory flow at 25%–75% of FVC ($FEF_{25\%-75\%}$), and FEV_1/FVC ratio. Percent predicted values were calculated based on the Third National Health and Nutrition Examination Survey III [14]. None of the participants received inhaled short-acting β_2-agonists and asthma controllers in the 12 hours prior to evaluation of lung function.

Skin prick test
Skin prick testing was performed with common aeroallergens, including house dust mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), *Alternaria*, dog, cat, cockroach, mugwort, ragweed, Japanese hop, grasses mix, and a 2-tree pollen mix). The longest and orthogonal diameters of the wheal were measured, and those with a mean wheal of at least 3 mm were considered positive. Atopy was defined as sensitivity to at least more than one common aeroallergen.

Asthma Control Test
We used the Korean version of the Asthma Control Test (ACT) or childhood ACT (C-ACT) questionnaire. The ACT survey is a patient-completed questionnaire with 5 items. Each item includes 5 response options corresponding to a 5-point Likert-type rating scale (total score range, 5 to 25). The participants along with their parents completed the C-ACT, and the questionnaire was scored as the sum of the responses of 7 items. On their own or with a caregiver's guidance, the child selects a frowning to smiling face with a score from 0

to 3, respectively, in response to 4 questions regarding the intrusiveness of their asthma symptoms. Further, the parents respond to 3 additional questions regarding the child's condition at home prior to the regular check-up. These 3 questions are scored on a 5-point Likert-type rating (total score range, 0 to 27). Children and parents were encouraged to discuss their problems or doubts in completing the questionnaire. A score of 20 or more in ACT or C-ACT indicated an adequately controlled asthma.

Asthma exacerbation
Participants were found to have AE if they had (1) a diagnosis of acute AE based on Global Initiative for Asthma guideline had been made by the participant's doctor at the clinic, (2) AE with use of systemic steroid or step-up of asthma controller, (3) a history of hospitalization, emergency department visit, unscheduled visit, or school absence due to asthma, (4) loss of asthma control on ACT, (5) a history of asthma symptoms, with frequent visits to the nurse's office resulting in limited or reduced school activities, and distressing symptoms even with self-rescuer medication.

Statistical analysis
Demographic and clinical data were presented as means and standard deviation as continuous variables. Differences among patients according to allergic disease, spirometry, or FeNO level were compared by using Fisher exact or χ^2 test, Mann-Whitney, or t tests, as appropriate. FeNO values were logarithmically transformed to assume a normal distribution and expressed as geometric means (GMs) with 95% confidence intervals (CIs). A p value <0.05 was considered significant. Statistical analyses were performed using the commercially available IBM SPSS Statistics ver. 25.0 (IBM Co., Armonk, NY, USA).

RESULTS

Patient characteristics
Among the 170 study participants, 160 students (94.1%) completed the 1-year regular follow-up and FeNO measurement every season. The reasons for the dropout were (1) a change in school (n = 4), (2) poor accomplishing spirometry test (n = 4), and (3) frequent school absence (n = 2). The demographic and clinical characteristics are shown in **Table 1**. A total of 36 children (22.5%) were diagnosed as asthmatic or had recurrent wheezing episodes. The proportion of children with allergic rhinitis and atopic dermatitis was 39.4% and 20.0%, respectively. Sixty-four children (40%) had inhalant allergen sensitization.

Table 1. The demographic and clinical characteristics of subjects (n = 160)

Characteristic	Value
Sex, male:female	76:94
Age (yr)	9.40 ± 1.48
Diagnosis of atopic dermatitis	32 (20.0)
Diagnosis of allergic rhinitis	63 (39.4)
Diagnosis of asthma or recurrent wheeze	36 (22.5)
Acute wheezing exacerbation within 1 year	14 (8.8)
Sensitization with inhalant allergen	64 (40.0)
FEV$_1$ (L)	1.67 ± 0.32
%predicted FEV$_1$	94.8 ± 13.2

Values are presented as mean ± standard deviation or number (%).
FEV$_1$, forced expiratory volume in 1 second.

AE and allergic disease status

During 1 year of the study period, 26 students (16.3%) had experienced AE. There was no significant difference in age, comorbid allergic disease except allergic rhinitis, wheezing-associated illness, and inhalant allergen sensitization between the children with AE and children without AE (**Table 2**). However, allergic rhinitis and male gender were significantly higher in children with AE ($p = 0.046$ and $p = 0.037$, separately). A total of 6 students (3.8%) experienced school absences due to AE.

Pulmonary function, FeNO, and AE

The baseline spirometry and FeNO monitoring values are listed in **Table 3**. Baseline FEV_1 did not significantly differ between children with AE and children without AE. However, baseline FEV_1/FVC and %predicted $FEF_{25\%-75\%}$ were significantly lower in children with AE than children without AE (both, $p < 0.05$). Proportion of children with %predicted $FEV_1 < 80\%$, $FEV_1/FVC < 80\%$ were higher in children with AE ($p < 0.01$, $p < 0.001$, respectively).

GM of the FeNO level did not significantly differ between children with AE and children without AE. Although not significant, the FeNO GM trended higher in children with AE (22.9 ppb vs. 19.9 ppb) than in children without AE. However, a high proportion of children with AE had a maximal FeNO ≥ 35 ppb during the study period ($p < 0.01$).

Pulmonary function, FeNO, and AE in children with inhalant allergen sensitization

Of 64 children with inhalant allergen sensitization, 14 (21.8%) had AE. The spirometry and FeNO values in these children are listed in **Table 4**. There was a significant difference in

Table 2. Characteristics of children with and without asthma exacerbation (AE) within 1 year

Variable	Children with AE (n = 26)	Children without AE (n = 134)	p value
Sex, male:female	17:9	59:75	0.046
Age (yr)	9.1 ± 1.7	9.5 ± 1.4	0.198
Diagnosis of asthma or recurrent wheeze	5 (19.2)	31 (23.1)	0.663
Wheezing exacerbation within the previous 1 year	3 (11.5)	11 (8.2)	0.582
Diagnosis of atopic dermatitis	7 (26.9)	25 (18.7)	0.335
Diagnosis of allergic rhinitis	15 (57.7)	48 (35.8)	0.037
Sensitization with inhalant allergen	14 (53.8)	50 (37.3)	0.115

Values are presented as mean ± standard deviation or number (%).

Table 3. Spirometry and FeNO level of children with and without AE within 1 year

Variable	Children with AE (n = 26)	Children without AE (n = 134)	p value
FEV_1	1.83 ± 0.35	1.86 ± 0.34	0.223
%predicted FEV_1	91.1 ± 13.0	94.8 ± 17.9	0.074
%predicted $FEV_1 < 80\%$	8 (30.8)	14 (10.4)	0.006
FEV_1/FVC (%)	87.9 ± 8.5	91.1 ± 5.4	0.015
$FEV_1/FVC < 80\%$	6 (23.1)	3 (2.2)	<0.001
$FEF_{25\%-75\%}$	1.90 ± 0.72	2.18 ± 0.56	0.030
%predicted $FEF_{25\%-75\%}$	88.1 ± 34.3	98.3 ± 20.4	0.047
%predicted $FEF_{25\%-75\%} < 70\%$	10 (38.5)	30 (22.4)	0.083
Mean FeNO (ppb), GM (95% CI)	16.5 (13.1–20.6)	13.5 (12.4–14.7)	0.070
Maximal FeNO (ppb), GM (95% CI)	22.9 (17.8–29.4)	18.8 (17.1–20.8)	0.116
Maximal FeNO ≥ 35 ppb	8 (30.8)	10 (7.5)	0.001
Mean FeNO ≥ 25 ppb	7 (26.9)	19 (14.2)	0.107

Values are presented as mean ± standard deviation or number (%) unless otherwise indicated.
FeNO, fractional exhaled nitric oxide; AE, asthma exacerbation; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; $FEF_{25\%-75\%}$, forced expiratory flow at 25%–75% of FVC; GM, geometric mean; CI, confidence interval.

Table 4. Characteristics, spirometry and FeNO level of children with and without AE among children with inhalant allergen sensitization

Variable	Children with AE (n = 14)	Children without AE (n = 50)	p value
Sex, male:female	13:1	25:25	0.004
FEV_1	1.63 ± 0.31	1.71 ± 0.30	0.388
%predicted FEV_1	94.6 ± 13.6	94.8 ± 11.6	0.962
%predicted FEV_1 < 80%	2 (14.2)	3 (6.0)	0.307
FEV_1/FVC (%)	88.0 ± 9.3	90.1 ± 6.0	0.325
FEV_1/FVC < 80%	3 (21.4)	1 (2.0)	0.008
$FEF_{25\%-75\%}$	1.91 ± 0.75	2.22 ± 0.58	0.104
%predicted $FEF_{25\%-75\%}$	93.6 ± 40.1	99.0 ± 23.0	0.533
%predicted $FEF_{25\%-75\%}$ < 70%	4 (28.6)	12 (24.0)	0.727
Mean FeNO (ppb), GM (95% CI)	20.1 (14.2–20.6)	20.0 (17.2–23.4)	0.977
Maximal FeNO (ppb), GM (95% CI)	29.2 (20.1–42.4)	28.8 (24.3–34.1)	0.943
Maximal FeNO ≥ 35 ppb	7 (50.0)	10 (20.0)	0.005
Mean FeNO ≥ 25 ppb	6 (42.8)	19 (38.0)	0.742

Values are presented as mean ± standard deviation or number (%) unless otherwise indicated.
FeNO, fractional exhaled nitric oxide; AE, asthma exacerbation; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; $FEF_{25\%-75\%}$, forced expiratory flow at 25%–75% of FVC; GM, geometric mean; CI, confidence interval.

sex, the proportion of children with FEV_1/FVC < 80%, and maximal FeNO ≥ 35 ppb between children with AE and children without AE. AE was more common in male than female children with inhalant allergen sensitization. There was no significant difference in FeNO levels between children with AE and children without AE. However, a significantly high proportion of children with AE had a maximal FeNO ≥35 ppb ($p < 0.05$). Although there were few children with FEV_1/FVC < 80%, this indicator was also associated with AE among children with inhalant allergen sensitization ($p < 0.01$).

Pulmonary function, exhaled nitric oxide, and AE in children without inhalant allergen sensitization

Of 96 children without inhalant allergen sensitization, 12 (12.5%) had AE. Each spirometric parameter (%predicted FEV_1, FEV_1/FVC, %predicted $FEF_{25\%-75\%}$) had a significant difference between children with AE and children without AE. Half of the children with AE had levels of less than 80% of % predicted FEV_1. It was also associated with AE among children without inhalant allergen sensitization (**Table 5**).

Table 5. Characteristics, spirometry and FeNO level of children with and without AE among children without inhalant allergen sensitization

Variable	Children with AE (n = 12)	Children without AE (n = 84)	P value
Sex, male:female	4:8	34:50	0.758
FEV_1	1.57 ± 0.39	1.68 ± 0.32	0.327
%predicted FEV_1	85.9 ± 16.1	96.1 ± 13.2	0.017
%predicted FEV_1 < 80%	6 (50.0)	11 (13.1)	0.002
FEV_1/FVC (%)	87.6 ± 8.0	91.6 ± 5.4	0.021
FEV_1/FVC < 80%	3 (25.0)	2 (2.4)	0.001
$FEF_{25\%-75\%}$	1.90 ± 0.71	2.16 ± 0.55	0.145
%predicted $FEF_{25\%-75\%}$	82.3 ± 27.3	98.0 ± 18.9	0.014
%predicted $FEF_{25\%-75\%}$ < 70%	6 (50.0)	18 (21.4)	0.033
Mean FeNO (ppb), GM (95% CI)	13.0 (10.0–16.9)	10.7 (10.0–11.3)	0.166
Maximal FeNO (ppb), GM (95% CI)	17.3 (12.9–23.1)	14.7 (13.5–15.9)	0.127
Maximal FeNO ≥ 35 ppb	1 (8.3)	0 (0)	0.125
Mean FeNO ≥ 25 ppb	1 (8.3)	0 (0)	0.125

Values are presented as mean ± standard deviation or number (%) unless otherwise indicated.
FeNO, fractional exhaled nitric oxide; AE, asthma exacerbation; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; $FEF_{25\%-75\%}$, forced expiratory flow at 25%–75% of FVC; GM, geometric mean; CI, confidence interval.

DISCUSSION

Exhaled nitric oxide has been extensively investigated as a noninvasive marker of airway inflammation in asthma. Eosinophilic inflammation in the airway increases exhaled nitric oxide that can be easily monitored in small amounts of exhaled breath from asthmatics. Since childhood asthma is more atopic than adult asthma, FeNO is proven to be effective in diagnosing childhood asthma. However, its predictive value about control and prognosis in children has not been sufficiently evaluated [8, 10].

We found that a greater number of children with AE had FeNO levels ≥ 35 ppb as compared to children without AE. However, there were no significant differences in the GM of the FeNO level between the 2 groups. Atopy and comorbid allergic diseases correlated with elevated FeNO levels. Nonatopic asthmatic children showed low levels of FeNO during a study period. Although a substantial portion of atopic children was not yet diagnosed with asthma, a sizable portion of these patients showed increased FeNO levels during the study period. Allergic rhinitis is a known risk factor for the development of asthma [15, 16].

In this study, 26 children (16.3%) had a higher incidence of AE than asthma prevalence from other study in Korean children [6]. School-based surveys face potential selection bias resulting from consenting parents who have a greater interest in their child's health. A high incidence also accounted for industrial regional characteristics, regular, and precise checkups in school by an allergy specialist. Interestingly, only 5 children with AE were previously diagnosed as asthmatic or with recurrent wheeze. The comorbidity of asthma and allergic rhinitis is remarkably high. Childhood asthma used to be underdiagnosed due to a lack of symptom recognition and awareness when children were younger. The diagnosis of allergic rhinitis was significantly higher in children with AE than in children without AE. Ten children with no diagnosis of asthma but with the diagnosis of allergic rhinitis had AE and seasonal allergen sensitivity. Concomitant air pollutants with the seasonal change in Korea could have likely influenced this AE. However, since we lacked data on inhalant allergen and air pollution exposure and had only a small number of children with AE in our study, we could not examine this further.

FeNO levels were higher in children with allergic rhinitis compared to children in the control group and showed a significant correlation with PC_{20} (provocative concentration causing a 20% fall in FEV_1) levels [17]. The relationship between increased FeNO in children with allergic rhinitis and onset of symptomatic asthma should be further studied in a long-term prospective study. In children and adults with atopic asthma, FeNO level > 300% of expected normal (approximately 35–50 ppb depending on individual factors) predicting both impairment with excessive use of short-acting bronchodilators and risk of exacerbations in the following year [18]. Increased FeNO level was previously associated with a relapse of asthma in children with clinical remission [19]. The highest FeNO measurement taken from serial measurements served as an independent predictor of the upcoming loss of asthma control in children with atopic asthma [20]. Current evidence suggests that FeNO values above the high cutoff (35–50 ppb) could be interpreted as a high degree of T-helper type 2-driven inflammation and a high likelihood of asthma diagnosis and an increased risk of worsening of symptoms and exacerbations in asthmatics with ongoing treatment [21]. Linn et al. [22] reported a high FeNO (≥35 ppb) in children is related to late-onset childhood asthma, low FEV_1, and FVC. Our findings were consistent with these studies.

The serial measurement of lung function is essential for the assessment of suspected chronic disease of the airways. Lung function, particularly FEV_1 as a percentage of predicted, is an important part of the assessment of future risk [8]. However, asthmatic children usually have relatively higher FEV_1 than asthmatic adults. As a result, $FEF_{25\%-75\%}$, FEV_1/FVC proves a more sensitive index of airway obstruction than FEV_1 in childhood asthma [23]. FEV_1/FVC ratio has nadir between 8 to 12 years during childhood and adolescence [24]. These findings suggest that FEV_1/FVC is a more predictive value than FEV_1 for AE. In our study, $FEV_1/FVC < 80\%$ had an association with AE for future risk, regardless of aeroallergen sensitization. In our study, the later FEV_1/FVC, $FEF_{25\%-75\%}$, and FEV_1 values were less in children with AE among children without aeroallergen sensitization. This finding suggests that pulmonary function measurements, rather than FeNO, provides a more predictive value of AE in children without aeroallergen sensitization.

The combination of spirometry and FeNO provided higher sensitivity and specificity for diagnosing asthma [25]. Higher FeNO and $FEV_1/FVC < 80\%$ significantly associated with asthma in school children [26]. In a previous clinical study, combined serial measurements of FeNO and $FEF_{25\%-75\%}$, rather than a snapshot measurement, may be more useful in monitoring asthma control and may play a role in the early detection of asthma progression [27]. Several studies have stratified patients with pediatric asthma or risk of future AE [28-30].

In this study, serial measurements of FeNO and FEV_1/FVC may play a role in the prediction of future exacerbated symptoms. We expect that prospective and more long-term monitoring will reveal more information about predicting AE. These findings may aid comprehensive asthma management and improve asthma control in school children.

There are several limitations to our study. First, our study could not check periodic spirometry during the study. Lung function is an integral part of the assessment of future risk. Although the proper spirometry interval remains unknown in children, current guidelines recommend periodically measurements for ongoing risk assessment [8]. Second, most AE and loss of control were obtained via a questionnaire based on the memory of parents and children despite annual physical examination by subspecialists, increasing the possibility of recall bias. Last, we speculate that we could not exclude the influence of individual exposure to smoking, air pollutant and inhalant allergen.

In conclusion, we showed that high FeNO values ≥ 35 ppb and the sensitive spirometric parameters such as FEV_1/FVC were associated with future AE. In particular, the maximal FeNO value of monitoring was associated with AE. The maximal value predicted AE in the whole study group, especially in cases of children with inhalant allergen sensitization. Because there was non-atopic asthma, spirometry should also be added to the toolkit for assessing or predicting asthma status and AE. In this regard, FeNO and spirometry-based risk stratification for predicting asthma may be beneficial for managing asthma in school children.

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