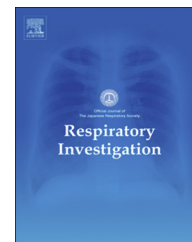




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Fractional exhaled nitric oxide levels as a predictor of long-term prognoses in patients with mild asthma



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ABSTRACT

Background: There is a growing belief that patients with bronchial asthma (BA) should be provided an individualized and optimized treatment plan. We aimed to clarify the predictors of long-term prognoses in patients with mild BA.

Methods: We conducted a retrospective study of consecutive patients who were newly diagnosed with mild BA at Iwate Medical University from 2011 to 2013, focusing on achievement of full asthma control based on the Asthma Control Test as an indicator of prognosis. Predictors were identified on the basis of a chart review.

Results: Among 71 patients with mild BA, 37 patients completed regular clinic visits for 1 year. Nineteen (51.4%) of these patients achieved full asthma control. Current smoking and the fractional exhaled nitric oxide (FeNO) level at the first patient visit were identified by multivariate logistic regression as possible predictors of the discontinuation of clinic visits and achievement of full asthma control, respectively. Low FeNO levels at the first clinic visit yielded a receiver operating characteristic-area under the curve of 0.860 (95% confidence interval [CI]=0.774–0.975) for the achievement of full asthma control. Using an FeNO cut-off level of 34 parts per billion yielded a sensitivity of 76.5% (95% CI=59.5–88.2%) and specificity of 73.7% (95% CI=58.5–84.2%).

Conclusion: Our preliminary results suggested that patients with newly diagnosed mild BA who display higher FeNO levels at their first clinic visits should be appropriately educated during early visits to receive optimal treatment and complete regular clinic visits.

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1. Introduction

Over the last decade, mild asthma has constituted the majority of asthma cases [1,2]. Mild asthma generally has a satisfactory long-term prognosis [3]. Monotherapy, using an inhaled corticosteroid (ICS), or an ICS in combination with a long-acting beta-agonist is also effective for the treatment of mild asthma, as well as moderate-to-severe asthma [4]. Once asthma is adequately controlled, step-down of the ICS dosage is recommended to avoid adverse effects, followed by withdrawal, if possible [5–10]. Individualization of asthma care is essential for ensuring optimal asthma treatment in each patient, as responsiveness to ICS therapy varies among patients [11]. It has been reported that approximately 20% of patients with mild asthma, which includes cough variant asthma (CVA), achieved successful withdrawal from ICS therapy [12,13]. In contrast, mild asthma tends to be underdiagnosed, undertreated, and inadequately controlled, as many patients with mild asthma do not seek treatment, even though this can occasionally result in a severe asthma attack [1,2]. In clinical practice, clinic visits of patients with mild asthma are often self-discontinued. Among such patients, however, the characteristics of patients whose asthma therapy should normally be continued, given their asthmatic symptoms, remain to be elucidated. The predictors of long-term prognoses in patients with mild asthma would allow clinicians to provide early appropriate education to those who should continually receive asthma therapy, in order to prevent their discontinuation of clinic visits.

An increasing body of evidence suggests the clinical relevance of the fractional exhaled nitric oxide (FeNO) level in patients with asthma. The level of FeNO increases in proportion to the severity of bronchial wall inflammation or induced-sputum eosinophilia [14–17]. The FeNO level of patients at the first clinic visit has diagnostic value for asthmatic conditions [18]. In addition, increases in FeNO levels are associated with deterioration in asthma control, whereas FeNO levels can be reduced in a dose-dependent manner with anti-inflammatory treatment. However, the benefit of FeNO measurements to the reduction of maintenance treatment in asthma patients has not yet been fully established [19–21]. Furthermore, FeNO levels can be influenced by various factors, including smoking [22,23]. As FeNO is a simple, safe, and reproducible biomarker, additional applications of this biomarker in the clinical treatment of asthma are expected.

Limited information is available regarding the predictors of long-term prognoses in patients with mild asthma. In this study, we first aimed to identify a predictor of the self-discontinuation of regular clinic visits among patients with newly diagnosed mild asthma. Each patient was provided with an action plan, including an explanation of asthma cure and the subsequent stepping down or stepping up of treatment. Second, we sought to identify an early predictor of favorable and unfavorable prognoses in patients with mild asthma, based on the Asthma Control Test (ACT), and identified lower FeNO levels at the time of initial diagnosis of asthma as a possible predictor of full asthma control [24]. Our results may be useful for clinicians in creating

individualized treatment plans for patients with mild asthma during their early visits.

2. Patients and methods

2.1. Subjects

This retrospective study consisted of 71 consecutive patients who visited the general outpatient clinic in the Department of Pulmonary Medicine, Iwate Medical University Hospital, between January 2011 and January 2013. Patients were selected if they were newly diagnosed with mild asthma and if they had never received an ICS or had not taken anti-allergic medications within 3 months of their first visit to our clinic. Bronchial asthma (BA) was diagnosed as follows: (1) wheeze or cough for longer than a minimum of 3 months, (2) clinical efficacy of an ICS, and (3) any of a number of the criteria [25]. These were: [A] a positive indication of airway reversibility after inhalation of a short-acting β_2 agonist, [B] response to a provocative concentration of methacholine, or [C] sputum eosinophil counts $>3\%$ or FeNO levels >22 parts per billion (ppb). Mild asthma was defined as a forced expiratory volume within 1 s ($FEV_{1.0}$ predicted) of $>80\%$ at the first diagnosis of asthma. The patients had no abnormalities on chest radiographs or CT scans, and had no prior history of treatment for pulmonary disease. Patients with CVA were also included in the present study, whereas those with atopic cough were excluded. A treatment action plan for mild asthma, including asthma cure and the step-up and step-down strategy, was given to each patient at treatment commencement. According to the global initiative for asthma guidelines, once asthma is controlled for 3 months, a gradual reduction in maintenance therapy is attempted, in order to identify the minimum dose required to control asthma, in principle [3]. When the ACT score was 25, asthma was assumed as being fully controlled [26]. In patients who satisfied the criteria for full asthma control in 3 consecutive clinic visits shortly after the initiation of ICS, step-down was started earlier than 3 months after the initiation of ICS therapy [24]. Asthma exacerbation was defined as the continuation of symptoms for more than 2 consecutive days, including wheezing and expiratory dyspnea during the day, or nighttime awakenings attributable to asthma, or a decline in $FEV_{1.0}$ of more than 20% [27]. The ICS dosage was stepped up in patients who experienced asthma exacerbation. Patients were required to continue regular clinic visits for at least 1 year to confirm the absence of subjective and objective exacerbations of asthma, even if asthma therapy was withdrawn. Patients who achieved withdrawal from ICS therapy were additionally requested to continue intermittent visits for at least 1 year after the cessation of therapy. No patient required oral corticosteroids during the period of asthma treatment. The study was approved by the Ethics Committee of Iwate Medical University (H26-112, 06/11/2014).

2.2. Blood tests

Blood tests included peripheral blood eosinophil counts and evaluations of non-specific IgE and antigen-specific IgE levels

in serum. A radioallergosorbent test for antigen-specific IgE was performed for weeds, mites, house dust, cats, dogs, cedar, cypress, orchard grass, moths, and mixed molds. Non-specific IgE levels were measured by fluorescence enzyme immunoassay (UniCAP; Pharmacia & Upjohn, Uppsala, Sweden).

2.3. Pulmonary function tests

FVC, FEV_{1.0}, V50, and V25 were measured according to the American Thoracic Society (ATS) guidelines [28]. Values were also expressed as percentages of the predicted normal values calculated according to sex, weight, and age. Values are shown as the mean $\pm$ standard deviation (SD). For airway reversibility testing, a positive result was defined as an improvement in FEV_{1.0} of 200 mL and >12% from baseline, when measured 20 min after the inhalation of a short-acting β_2 agonist (salbutamol 200 μ g from a pressurized inhaler).

2.4. FeNO measurement

FeNO was measured in accordance with ATS/European Respiratory Society (ERS) recommendations using NIOX MINO[®] (Aerocrine AB, Solna, Sweden), and it was expressed as ppb. Briefly, measurements of FeNO were performed by asking the subjects to empty their lungs, inhale to their total lung capacity through a mouthpiece, and finally to exhale into the device at a constant flow rate of 50 mL/s. The software within the device automatically ensured that the breathing maneuver was performed according to ATS/ERC guidelines [29]. Calibration of the analyzer was automatically performed by the software. The sensor on the device was changed periodically according to the manufacturer's guidance. FeNO was measured before pulmonary function and airway hyperresponsiveness (AHR) testing.

2.5. AHR

AHR testing using methacholine was performed via the Astograph[®] method (Jupiter 21; Chest MI, Inc., Tokyo, Japan) according to the protocol described by Takishima et al. [30]. Briefly, AHR was tested by directly recording a dose–response curve of Rrs (cmH₂O L⁻¹ s⁻¹) during continuous inhalation of methacholine in 2-fold incremental concentrations (49–25,000 g/mL), under tidal breathing from nebulizers with an output of 0.15 mL/min. If bronchodilators were being used, their use was suspended 24 h before methacholine inhalation. Briefly, after we recorded the baseline Rrs during the inhalation of physiologic saline for 1 min, patients inhaled methacholine at 1-min intervals, starting with the lowest concentration. After methacholine inhalation, a continuous increase in Rrs was assumed to denote positive airway hypersensitivity. One unit of D_{min} is equivalent to the inhalation of 1 mg/mL methacholine for 1 min.

2.6. Induced sputum tests

Induced sputum was collected using the method described by Pin et al. [31], with the inhalation of 5 mL of 3% hypertonic saline using an ultrasonic nebulizer (Pari-Gerät, PARI GmbH,

Starnberg, Germany). The sputum samples were stained with May-Giemsa stain and examined by microscopy. Observers who counted the cells were blinded to the patients' treatment history. Eosinophilia in the induced sputum was defined as an eosinophil count of >3% of the total cell count.

2.7. Statistical analysis

Statistical significance of differences between 2 groups was evaluated using the Mann–Whitney *U* test or Fisher's exact test. Stepwise discriminant analysis was used to calculate risk factor coefficients as a multivariate logistic regression analysis. Spearman's rank correlation coefficient was used to evaluate the relationships of (1) FeNO levels at the first clinic visit with (2) the duration from the start of the last episode of asthma symptoms until the beginning of ICS treatment and (3) the percentages of sputum eosinophil counts. A *p* value of <0.05 was considered statistically significant. Receiver-operating characteristic (ROC) curves were plotted for FeNO levels and successful withdrawal from ICS therapy. The indicative accuracy of the level was assessed by calculating the area under the curve (AUC), as described elsewhere [32]. A diagnostic test with an AUC exceeding 0.75 was regarded as contributive [33]. Statistical analyses were performed using SPSS statistics software (IBM Japan, Tokyo, Japan).

3. Results

3.1. Characteristics of patients who continued or discontinued regular clinic visits

A total of 71 patients, aged 19–78 years, were enrolled in the present study. Eleven patients were admitted to other medical institutes and eliminated after diagnosis and initial treatment (Fig. 1). Twenty-three patients who were diagnosed with mild BA discontinued treatment after several visits. The remaining 37 patients continued to visit our office for at least 1 year. Patients who continued to visit the clinic were older than those who discontinued regular clinic visits (Table 1). The percentage of patients who were current smokers was significantly higher among patients who discontinued consultation than among those who continued treatment (Table 1). Current smoking was identified as a potential predictor of the discontinuation of regular clinic visits by multiple regression analysis (odds ratio=6.60, 95% confidence interval [CI]=1.423–30.572, *p*=0.016, Table 2).

3.2. Comparison of patients with fully controlled and uncontrolled asthma

Among the 37 patients who continued to visit the clinic, 18 patients did not continually achieve full asthma control, based on ACT score, and consequently required continuation of ICS therapy. The remaining 19 patients achieved full asthma control over 3 consecutive clinic visits, based on the ACT score, and withdrawal of asthma therapies was attempted. They started the withdrawal from ICS at 42.0 [36.0] days (mean [SD]) after the beginning of ICS therapy. Among these patients, 17 patients (89.9%) achieved

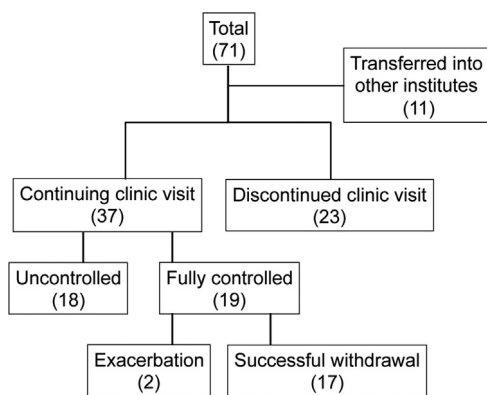


Fig. 1 – Patients included in the study. A total of 68 patients were enrolled in the present study. Eleven patients were transferred to other institutes after being newly diagnosed with mild asthma. Twenty-three of the remaining patients self-discontinued their regular clinic visits after the start of inhaled corticosteroid (ICS) therapy. The remaining 37 patients continued their regular clinic visits for more than 1 year. Nineteen patients achieved full asthma control and consequently attempted ICS withdrawal, but 2 of these patients experienced exacerbations of asthmatic symptoms. The remaining 17 patients achieved successful withdrawal from ICS therapy without exacerbations of asthma symptoms. Conversely, 18 patients did not achieve full asthma control, and they continually received asthma therapy.

successful withdrawal of ICS therapy after treatment cessation. These 17 patients experienced no exacerbation of asthmatic symptoms for at least 1 year (mean follow-up period: 23.4 [2.91] months). The 17 patients completed respiratory function tests at 1 year after the cessation of ICS therapy. After 1 year, FEV_{1.0} had not declined by more than 20% in any patient compared with that before the cessation of treatment. In contrast, ICS therapy was resumed in 2 patients because of the exacerbation of asthmatic symptoms. After re-treatment, the 2 patients regained full asthma control. Next, we attempted to identify an early predictor of the achievement of full asthma control as an indicator of good prognosis in patients with newly diagnosed mild asthma. Compared with the findings in patients with uncontrolled asthma, the duration from the onset of the last episode of asthmatic symptoms until the first clinic visit, the sputum eosinophil count, FeNO levels, and the daily dosage of ICS at the beginning of treatment were significantly smaller among the 19 patients who achieved full asthma control (Table 3). There was no difference in the intensity of asthma symptoms before treatment between the 2 groups. In univariate logistic regression analysis, FeNO levels at the first visit and the daily dosage of ICS at the beginning of treatment were associated with full asthma control (Table 4). In addition, FeNO levels at the first visit were identified as a possible predictor of full asthma control by multivariate logistic regression (odds ratio=0.9457, 95% CI=0.9017–0.9919, *p* value=0.021). In ROC curve analysis based on the results of the 37 patients who continued regular treatment, FeNO levels at the first clinic visit displayed an AUC of 0.860 (95% CI=0.774–0.975) for the achievement of full asthma control (Fig. 2). An FeNO cut-off level of 34 ppb

yielded a sensitivity of 76.5% (95% CI=59.5–88.2%) and specificity of 73.7% (95% CI=58.5–84.2%).

3.3. The relationship of FeNO levels with other clinical characteristics

We considered the clinical implications of FeNO levels at the time of asthma diagnosis being predictive of the prognosis of patients with mild asthma. We thus explored the relationship of FeNO levels with other clinical characteristics of asthma. First, the relationship between FeNO levels and responsiveness to ICS therapy was estimated. Poor responsiveness to ICS treatment was only observed in 4 patients who had achieved full asthma control, but the proportion of patients with poor responsiveness did not differ between the 2 groups (0% vs. 21.1%, *p*=0.105; Fig. 3A). The 4 patients with poor responsiveness to ICS treatment exhibited extremely low FeNO levels, and their symptoms were relieved by the temporal administration of leukotriene antagonists. In the present study, FeNO levels were not significantly different between current smokers and non-smokers for each subgroup classification, including asthma control and clinic visit continuation (Fig. 3B). Moreover, a moderate correlation was observed between FeNO levels and sputum eosinophil counts (*r*=0.613, *p*<0.001, Fig. 4).

4. Discussion

In the present study, we attempted to identify early predictors of self-discontinuation of regular clinic visits and the achievement of full asthma control. Asthma severity was previously defined using pulmonary function tests, such as FEV_{1.0}% predicted, although the difficulty of controlling asthma by treatment has recently been used to define asthma severity [27]. It would have been difficult to formulate an individualized treatment plan during early clinic visits if the latter criterion was used for this study. Therefore, we used FEV_{1.0}% predicted at the first clinic visit as the definition of mild asthma in the present study, although patients with moderate asthma meeting the latter criterion may have been included.

In the present study, a lower FeNO level at the first clinic visit was identified as a possible predictor of full asthma control in patients with mild asthma. Based on multivariate regression analyses, the clinical utility of FeNO levels in our study is consistent with previous findings in patients with moderate-to-severe asthma [10]. Furthermore, based on the results of ROC–AUC analysis, FeNO levels assessed at the first clinic visit were predictive of full asthma control. In ROC curve analysis, an FeNO level of 34 ppb yielded the greatest sensitivity and specificity. The finding that lower FeNO levels in patients with newly diagnosed mild asthma are associated with full asthma control may be due to two possible reasons. First, it is possible that earlier ICS intervention in patients with mild asthma could result in better control of prolonged inflammation in the airway than delayed intervention. In our study, among patients lacking full control of asthma, the duration from the onset of the last episode of asthmatic symptoms until the first clinic visit was statistically significantly shorter than in patients with full asthma control. It

Table 1 – Comparison of patients who continued versus self-discontinued clinical visitations.

N	Continuing clinic visit 37	Self-discontinued visit 23	p Value
Age (yr)	50.9±15.6	42.1±15.8	<0.05
Female (%)	21 (57.0)	11 (47.8)	n.s
Body Mass Index (kg/m ²)	22.6±3.5	23.0±3.0	n.s
Current Smoker (%)	4 (10.8)	11 (47.8)	<0.01
Classification in symptom intensity ^a (Class 1/2/3/4)	1/12/15/9	0/9/10/4	n.s
Duration until the first clinic visit (day) ^b	157.0±268.3	64.2±153.2	n.s
Peripheral blood eosinophil count (/μl)	0.27±0.28	0.21±0.16	n.s
Serum total IgE (IU/ml)	237.5±409.2	203.4±244.4	n.s
Mite-specific IgE (IU/ml)	9.46±23.3	15.4±30.3	n.s
Sputum eosinophil count (%)	0.35±0.34	0.28±0.31	n.s
FeNO (ppb)	42.2±31.9	34.8±15.8	n.s
Pulmonary function tests			
FEV1.0, %predicted	106.3±16.7	103.2±14.0	n.s
FEV1.0/FVC	85.3±4.4	87.3±5.3	n.s
%V50	89.5±28.7	84.0±27.7	n.s
%V25	82.6±42.8	83.6±34.2	n.s
Comorbidity			
Rhinitis (%)	15 (40.5)	12 (37.5)	n.s
Chronic sinusitis (%)	3 (8.1)	1 (3.1)	n.s
GERD (%)	6 (16.2)	1 (3.1)	n.s
Treatment			
Initial dose of ICS (μg/daily) ^c	491.9±215.1	525.0±175.0	n.s
Leukotriene receptor antagonist patient number (%)	4 (11.8)	2 (8.7)	n.s

^a Classification in symptom intensity indicates the intensity of asthmatic symptoms before the treatment for asthma. Class 1: day and night symptoms are under one time a week and two times a month, respectively. Class 2: day and night symptoms are more than one time a week and two times a month, respectively. Class 3: day symptoms are daily and night ones are more than one time a week. Class 4: day symptoms are continuous and night ones are frequent. Abbreviation; GINA: global initiative for asthma, FeNO: fractional exhaled nitric oxide, GERD: gastroesophageal reflux disease.

^b The duration indicates the interval from the beginning of asthmatic symptoms until the first clinic visit.

^c Converted to fluticasone propionate equivalent.

Table 2 – Results of univariate and multivariate logistic regression analysis for continuation of regular clinic visits.

Variable	Univariate			Multivariate		
	Exponent	95% Confidence interval	p Value	Exponent	95% Confidence interval	p Value
Age	0.9665	0.9289–1.0056	0.097	0.9712	0.9305–1.0136	0.180
Current Smoking	7.2726	1.9425–27.2276	0.003	6.3715	1.3429–30.2311	0.020

has been reported previously that early intervention may result in a better prognosis in patients with mild asthma [34].

The second possibility is that the group of patients who displayed low FeNO levels differed from the group of patients with higher FeNO levels because of the pathophysiology of their asthma. McGrath et al. reported that half of the patients with mild-to-moderate asthma have a non-eosinophilic type of airway inflammation that typically displays poor responsiveness to ICS treatment [35]. In our study, we identified 4 patients whose asthma was poorly controlled on ICS therapy, and these patients had extremely low FeNO levels at the time of diagnosis. Symptoms were relieved in these patients via the administration of leukotriene antagonists, and they were included in the full asthma control group, although the proportion of patients who responded poorly to ICS therapy did not differ significantly between the uncontrolled and fully controlled asthma groups. In a larger study, it should be confirmed whether patients with full asthma

control differ from those with uncontrolled asthma in terms of the clinical characteristics and the pathogenesis of their asthma. In contrast, FeNO levels were moderately correlated with sputum eosinophil counts in the present study, which was consistent with previous reports [36].

In the present study, approximately 40% of patients with newly diagnosed mild asthma discontinued their regular clinic visits, despite the presentation of an action plan, including asthma cure and withdrawal from treatment. In total, 11 (45%) of these 23 patients had FeNO levels >34 ppb, and the continuation of ICS therapy may be essential for these patients. We evaluated the risk factors for discontinuation, and current smoking was identified as a predictor of self-discontinuation. In support of our observation, it has been reported that smoking is a predictive factor for non-compliance with the administration of asthma medication [37]. Therefore, smokers who are newly diagnosed with mild asthma should be educated to continue asthma treatment,

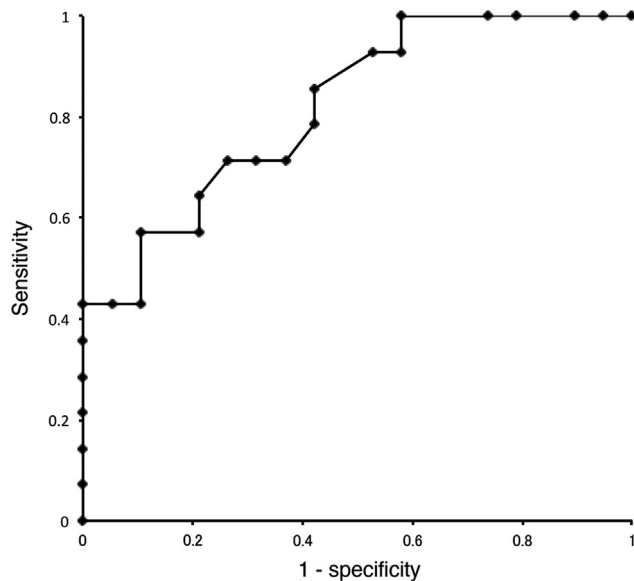


Fig. 2 – Receiver-operating characteristic (ROC) curve analysis was used to assess the diagnostic validity of fractional exhaled nitric oxide (FeNO) levels in predicting full asthma control based on the Asthma Control Test score in patients with newly diagnosed mild asthma. The area under the curve was 0.860 (95% confidence interval [CI]=0.774–0.975) for full asthma control. An FeNO level cut-off of 34 ppb was associated with a sensitivity of 76.5% (95% CI=59.5–88.2%) and a specificity of 73.7% (95% CI=58.5–84.2%).

and a special effort should be made to encourage the cessation of cigarette smoking.

In the present study, 17 of the 19 patients (89.5%) with newly diagnosed mild asthma who exhibited full asthma control achieved successful withdrawal of ICS therapy, without asthma exacerbation, after the cessation of ICS or leukotriene antagonist treatment, suggesting that these patients do not necessarily require continuous asthma treatment. Tsurukisawa et al. reported possible predictors of successful reductions in ICS dosage in patients with persistent moderate-to-severe persistent asthma using comparisons between patients with and without increasing exacerbation after the cessation of ICS therapy [10]. In their publication, 55.6% of patients who halted ICS therapy did not experience an exacerbation of asthma. Predictors of successful withdrawal from ICS therapy included the duration of the absence of clinical symptoms before ICS reduction, acetylcholine PC20, FeNO, and FEV_{1.0} before withdrawal from ICS treatment. The authors stressed the importance of long-term ICS administration for the adequate control of airway inflammation in patients with moderate-to-severe asthma. Compared to that in the data provided by Tsurukisawa et al., the exacerbation rate after ICS treatment cessation was markedly lower in our study [10]. We speculate that the difference in exacerbation frequency is attributable to asthma severity and disease duration. In future, a predictor of long-term successful withdrawal from ICS therapy in patients with mild asthma should be sought.

The present study had some limitations. First, the study population was relatively small, although our results were

Table 3 – Comparison between uncontrolled and totally controlled groups.

N	Uncotrolled 18	Totally controlled 19	p Value
Age (yr)	49.2±15.9	52.2±15.7	n.s
Female (%)	12 (66.6)	13 (76.7)	n.s
Body Mass Index (kg/m ²)	22.8±2.9	22.4±4.0	n.s
Current smoker	3 (16.6)	1 (5.3)	n.s
Classification in symptom intensity ^a (Class 1/2/3/4)	0/5/7/6	1/7/8/3	n.s
Duration until the first clinic visit (Day) ^b	252.4±317.9	66.6±166.1	<0.01
Peripheral blood eosinophil count (μl)	0.33±0.37	0.16±0.07	n.s
Serum total IgE (IU/ml)	374.8±551.6	115.2±146.5	n.s
Mite-specific IgE (IU/ml)	18.0±30.9	1.8±3.8	n.s
Sputum eosinophil count (%)	45.7±31.7	23.7±25.7	<0.05
FeNO (ppb)	60.7±35.0	24.9±14.5	<0.01
Pulmonary function tests			
FEV1.0, %predicted	103.9±18.9	109.1±13.1	n.s
FEV1.0/FVC	84.8±3.9	86.1±7.1	n.s
%V50	84.3±24.8	94.7±29.0	n.s
%V25	74.8±31.1	90.4±55.8	n.s
Comorbidity			
Rhinitis (%)	10 (55.6)	5 (26.3)	n.s
Chronic sinusitis (%)	4 (22.2)	1 (5.3)	n.s
GERD (%)	1 (5.6)	2 (10.5)	n.s
Treatment			
Initial dose of ICS (μg/daily) ^c	583.3±250.0	405.3±124.5	<0.05
Leukotriene receptor antagonist patient number (%)	0 (0)	4 (21.1)	n.s

Abbreviation; GINA: global initiative for asthma, FeNO: fractional exhaled nitric oxide, GERD: gastroesophageal reflux disease.

^a Classification in symptom intensity indicates the intensity of asthmatic symptoms before the treatment for asthma. Class 1: day and night symptoms are under one time a week and two times a month, respectively. Class 2: day and night symptoms are more than one time a week and two times a month, respectively. Class 3: day symptoms are daily and night ones are more than one time a week. Class 4: day symptoms are continuous and night ones are frequent.

^b The duration is the interval from the beginning of asthmatic symptoms to the first clinic visit.

^c Converted to fluticasone propionate equivalent.

statistically significant. Our results should be validated in a larger cohort study. Second, the mean follow-up period after the cessation of ICS therapy was 23.5 months, which was relatively short. In particular, the 4 patients who were diagnosed with seasonal BA should be followed for a minimum of 3–5 years, because seasonal antigen levels related to weeds can vary greatly from year to year. Third, we could not explore the significance of airway hypersensitivity tests as predictors of full asthma control, because the number of patients who completed the test was insufficient to power statistical analyses. It would be interesting to elucidate whether there were any differences in the characteristics of

Table 4 – Results of univariate and multivariate logistic regression analysis for totally controlled asthma.

Variable	Univariate			Multivariate		
	Exponent	95% Confidence interval	p Value	Exponent	95% Confidence interval	p Value
Duration until the first clinic visit ^a	0.9977	0.9947–1.0006	0.114			
Sputum eosinophil counts	0.2450	0.0500–1.2016	0.083			
FeNO	0.9834	0.9682–0.9989	0.036	0.9459	0.9024–0.9915	0.021
ICS dosage (daily) ^b	0.9944	0.9893–0.9994	0.028	0.9965	0.9911–1.0018	0.192

Abbreviation; FeNO: fractional exhaled nitric oxide, ICS: inhaled corticosteroid.
^a The duration is the interval from the beginning of asthmatic symptoms to the first clinic visit.
^b Converted to fluticasone propionate equivalent.

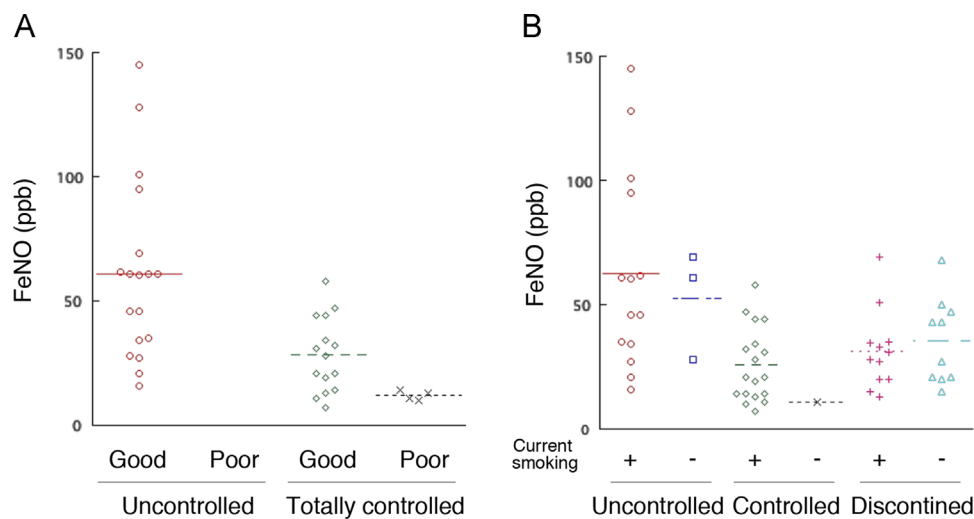


Fig. 3 – Relationship between fractional exhaled nitric oxide (FeNO) and other clinical characteristics in patients with mild asthma. (A) FeNO and responsiveness to inhaled corticosteroid (ICS) therapy in the uncontrolled and fully controlled asthma groups. Poor responsiveness to ICS treatment was observed in 4 patients in the latter group. These 4 patients displayed low levels of FeNO. (B) A comparison of FeNO levels between non-/ex-smokers and current smokers is shown. There was no difference between the two groups.

airway hypersensitivity between patients with mild asthma and less airway remodeling, and those with moderate-to-severe asthma and progressive remodeling. Fourth, it was difficult to determine the actual duration from the onset of the last episode of asthmatic symptoms until the first clinic visit. The duration was shorter than 3 months in 23 patients with mild asthma, and the shortest duration was 5 days. During a detailed patient interview, patients stated that they intermittently experienced asthmatic symptoms during the past few years, but that they did not seek medical attention. ICS administration was indispensable in patients with a shorter duration, because the intensity of asthma symptoms was >2 , even in such patients. Fifth, we could not follow FeNO levels in all patients throughout the treatment course, as this study was retrospectively performed.

5. Conclusions

We found that current smoking and higher FeNO levels at the time of the first clinic visit are possible predictors of the self-discontinuation of regular clinic visits and unfavorable

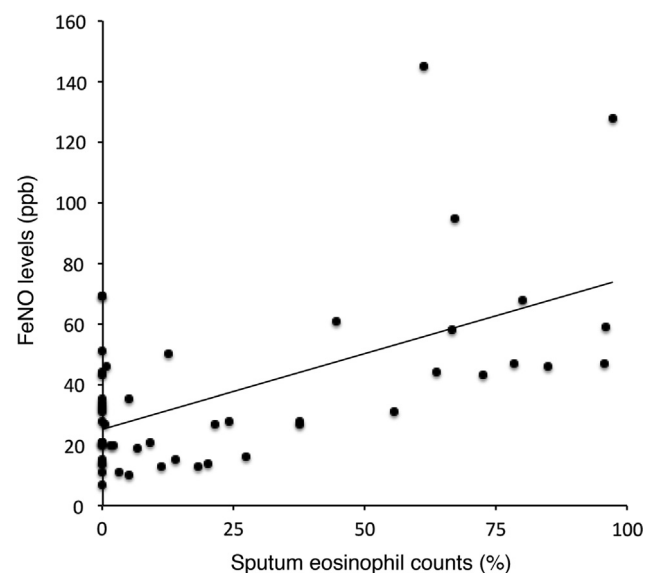


Fig. 4 – The correlation between fractional exhaled nitric oxide (FeNO) levels and sputum eosinophil counts. A moderate correlation was observed between FeNO levels and sputum eosinophil counts ($r=0.613$, $p<0.001$).

prognoses in patients with newly diagnosed mild BA. Our preliminary results may facilitate creation of individualized treatment plans for patients with mild asthma and prevent the discontinuation of regular clinic visits and inadequate treatment in patients with mild asthma.

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Conflict of interest

The authors have no conflicts of interest to declare.

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