Repeated Fractional Exhaled Nitric Oxide Measurements Is Not Essential for Asthma Screening

Running title: Utility of repeated measurements of FeNO

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ABSTRACT

Background: Although older guidelines recommend that fractional exhaled nitric oxide (FeNO) should be checked more than twice during the same session for an asthma diagnosis, recent studies showed the excellent reproducibility of FeNO measurements.

Objective: We aimed to determine whether repeated FeNO measurements during the same session are necessary for asthma screening.

Methods: We retrospectively reviewed the electronic medical records of adult outpatient subjects who visited the pulmonary department for an asthma diagnosis and assessed FeNO measurements obtained from June 2016 to July 2017.

Results: Among the total of 132 enrolled patients, 79 patients (59.8%) were diagnosed with asthma. Repeated FeNO measurements taken during the same session showed high reproducibility (intraclass correlation coefficient > 0.9; $P < 0.001$) and a strong correlation (Pearson's coefficient > 0.9; $P < 0.001$); however, the reproducibility and correlation were slightly weaker in subjects with low FeNO values. The value of repeated measurement was not significantly different each other in general; however, the second FeNO measurement was significantly higher than the first measurement in subjects with the lowest and highest lung function. The predictive power of FeNO for asthma measured the first time (sensitivity, 80.5%; specificity, 85.1%) was not inferior to that measured the second time (sensitivity, 76.6%; specificity 85.1%) or the even geometric mean of the two.

Conclusion: Repeated FeNO measurement during the same session is not essential for asthma screening in cases when the first acceptable FeNO measurement is performed using the proper method.

Keywords: Asthma, Fractional Exhaled Nitric Oxide, Repeated measurements

RESUMEN

Antecedentes:

Aunque las guías más antiguas recomiendan que el óxido nítrico exhalado (FeNO) se determine más de dos veces en la misma sesión para el diagnóstico de asma, algunos estudios recientes han demostrado la excelente reproducibilidad de las mediciones de FeNO.

Objetivo:

Nuestro objetivo fue determinar si las mediciones repetidas de FeNO durante la misma sesión son necesarias para el cribado del asma.

Métodos:

Revisamos retrospectivamente los registros médicos electrónicos de pacientes adultos ambulatorios que visitaron el departamento de neumología para confirmar un diagnóstico de asma durante los meses de junio de 2016 a julio de 2017, y se evaluaron las mediciones de FeNO obtenidas.

Resultados:

De un total de 132 pacientes estudiados, 79 pacientes (59,8%) fueron diagnosticados con asma. Las mediciones repetidas de FeNO tomadas durante la misma sesión mostraron una alta reproducibilidad (coeficiente de correlación intraclase> 0,9; p <0,001) y una fuerte correlación (coeficiente de Pearson> 0,9; p <0,001); sin embargo, la reproducibilidad y la correlación fueron ligeramente más débiles en sujetos con valores bajos de FeNO. El valor de la medición repetida no fue significativamente diferente entre sí en general; sin embargo, la segunda medición de FeNO fue significativamente más alta que la primera medición en sujetos con valores de la función pulmonar más bajos y más altos. El poder predictivo de FeNO para el diagnóstico de asma medido la primera vez (sensibilidad, 80.5%; especificidad, 85.1%) no fue inferior al medido la segunda vez (sensibilidad, 76.6%; especificidad 85.1%) o la media geométrica uniforme de los dos.

Conclusión: la medición repetida de FeNO durante la misma sesión no es esencial para el cribado del asma en los casos en que la primera medición de FeNO es aceptable y se realiza con el método adecuado.

Palabras clave: asma, óxido nítrico exhalado fraccional, mediciones repetidas

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INTRODUCTION

Fractional exhaled nitric oxide (FeNO) reflects eosinophilic airway inflammation and its level can be measured easily. Recently, the utility of FeNO has been demonstrated for the diagnosis and monitoring of asthma [1,2]. However, several personal characteristics and environmental factors are known to influence FeNO levels [3-6]. In addition, to obtain a reliable FeNO level, sufficient skill is needed to maintain a constant expiratory flow rate during the test. The 2005 American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines recommend performing FeNO measurements twice to obtain two values; the mean of the two values should then be used to interpret the test [7]. However, there has been no definite evidence to support this protocol. Recently, some studies showed the excellent reproducibility and repeatability of FeNO measurements and suggested that repeated FeNO measurements during the same session are unnecessary [8,9]. The utility of multiple FeNO measurements for asthma diagnosis has never been studied.

This study aimed to determine whether repeated FeNO measurements obtained during the same session are necessary for an asthma diagnosis.

METHODS

Patients and study designs

We retrospectively reviewed the electronic medical records of adult outpatients aged 18 years and older who visited the pulmonary department of Gangnam Severance Hospital. They were

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referred for FeNO measurements between June 2016 and July 2017 to diagnose suspected asthma. To assess repeatability, a subset of the participants underwent paired FeNO measurements during the same clinic visit. We collected medical records of enrolled subjects including baseline characteristics to define significant factors for FeNO level.

FeNO measurements

FeNO was measured using a handheld device (NObreath FeNO Monitor, Bedfont Scientific Ltd., England) during scheduled study visits according to ATS/ERS guidelines as shown below.[7] This device relies on an electrochemical sensor to detect exhaled NO levels and provides measurements from 5 to 300 parts per billion (ppb) in whole numbers. We requested that all subjects avoid eating, drinking, smoking, and strenuous exercise for 2 hours prior to the FeNO measurements to rule out biases. Moreover, the use of asthma drugs was forbidden unless the patient's physician instructed them otherwise.

The subjects exhaled fully while seated and then inhaled over 2 to 3 seconds to total lung capacity through a filter and exhaled with an upper airway pressure of 5 to 20 cmH_2O. Two successive FeNO measurements were performed at an interval of 4–5 min. All subjects exhaled against an airflow resistor for 10 seconds at a flow rate of 50 mL/s and the FeNO values were monitored on the screen of the device. Measurements were made before performing spirometry. The detection limit of the NObreath device is 5 ppb.

Lung function test and bronchodilator response test

Spirometry was carried out on the first study day after the FeNO measurements. Lung function

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tests were performed with a spirometer (Vmax, SensorMedics, Yorba Linda, CA, USA) in accordance with ATS/ERS recommendations [10]. The following variables were obtained from the best reproducible forced expiratory maneuvers: forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), and the FEV_1/FVC ratio. A significant improvement in lung function from bronchodilator use was defined as an improvement in the pre-bronchodilator FEV_1 of ≥ 12% and 200 mL after the administration of salbutamol (200 μg).

Methacholine challenge test

The methacholine challenge test was carried out using the standard five-breath dosimeter method recommended by the ATS [11]. Methacholine dilutions of 1, 4, 8, and 16 mg/mL were used. Spirometry was performed 30 seconds and 90 seconds after each inhalation. The test was finished when the FEV_1 value decreased by more than 20% from baseline. The positivity of the test was determined as a less than 16 mg/mL of a provocative concentration that resulted in a 20% decrease in FEV_1.

Asthma diagnosis

A diagnosis of asthma was made by clinicians based on the symptoms, physical examination, bronchodilator test, and methacholine test in all subjects according to the Global Initiative for Asthma standard [12].

Definition of a large gap and positivity in FeNO measurements

The upper quartile of subjects who showed a larger gap between the first and second

individual measurement values formed the large gap group. Moreover, a large gap was defined as more than a 17.5% difference in FeNO values between the two measurements. Although there are some concerns about the cut-off value for FeNO, we adopted 30 ppb in this study in consideration of previous studies, including a Korean study [13,14].

Statistics

All data analyses were performed using SPSS statistical analysis software (SPSS Inc., Chicago, IL, USA). The FeNO values appeared to be log-normally distributed; therefore, we used the geometric mean. The chi-squared test and t-test were used to assess differences in characteristics between subjects with and without a large gap. The intraclass correlation coefficient (ICC) and Pearson's correlation were used to assess the reproducibility and correlation between the first and second FeNO measurements. The significance of the difference in FeNO values between the first and second measurements was assessed using the paired t-test. The agreement rate between FeNO positivity and an asthma diagnosis was simply calculated. We found factors significant for the FeNO level using univariate and multivariate regression analyses among sex, age, height, weight, body mass index (BMI), pulmonary function variables, and asthma history. After adjustment for significant factors (absolute FVC and FEV_1), a receiver operating characteristic analysis was conducted to obtain the areas under the curve, sensitivities, and specificities of the first and second FeNO measurements, the geometric mean, the larger of the two values, and the smaller of the two values to predict asthma. A *P*-value less than 0.05 was considered statistically significant.

Ethics

This study was exempted from requiring approval by the Institutional Review Board of the Gangnam Severance Hospital, Yonsei University Health System.

RESULTS

Clinical characteristics of the enrolled subjects

Among the enrolled 132 subjects (mean age, 42.8 ± 16.0 years; men, 50.0%), 79 patients (59.8%) were diagnosed with asthma. The geometric mean values of the first and second FeNO measurements were 32.5 ppb and 33.4 ppb, respectively; there was no statistically significant difference between the two values (Table 1).

Determinants of a large gap in FeNO measurements

When we used 17.5% as the standard for a large gap between FeNO measurements, 33 subjects (25.0%) were classified into the large gap group. Sex, age, height, weight, and lung function were not significantly different between subjects with and without a large gap. Subjects with a large gap showed significantly higher BMI values than those without a large gap (P = 0.015). Asthma was significantly more prevalent in subjects without a large gap (66.7%) than in subjects with a large gap (39.4%; P = 0.005). Subjects with large gaps showed significantly lower FeNO values than those without large gaps (Table 1).

Reliabilities, correlations, and comparisons of FeNO measurements

In general, repeated FeNO measurements showed high reproducibility (ICC > 0.9; $P < 0.001$) and strong correlations (Pearson's coefficient > 0.9; $P < 0.001$); however, the reliability (ICC, 0.772–0.886) and correlation (Pearson's coefficient, 0.681–0.774) were slightly weaker in subjects with low FeNO levels (< 52.8 ppb) (Table 2; Figure 1A).

The first FeNO levels measured (32.5 ± 2.3 ppb) were not significantly different from those measured the second time (33.4 ± 2.3 ppb) (Figure 1B). However, the second measured FeNO values were significantly higher than those measured the first time in subjects with the poorest lung function (44.36 ppb vs. 40.60 ppb in subjects with the lowest FVC values, $P = 0.024$) (Table 2). This trend was also shown in subjects with the greatest lung function (30.74 ppb vs. 28.79 ppb in subjects with the highest FVC values, $P = 0.004$; 34.34 ppb vs. 32.50 ppb in subjects with the highest FEV_1 values, $P = 0.014$).

Predictability of FeNO measurements for asthma diagnosis using the agreement rate

When FeNO positivity was defined as greater than or equal to 30 ppb, the predictive power of FeNO measurement for asthma was excellent. Overall, the first measured FeNO value was not inferior to that measured the second time for asthma prediction in all subgroups (total agreement rate, 79.5% vs. 78.0%). Moreover, the total agreement rate for asthma using the first measurement value was not inferior to that using the numerical mean of the two values, the larger one of the first and second values, or the smaller one of the first and second values (Table 3).

Significant factors determining the FeNO value

In the univariate linear regression analysis, sex, height, weight, and BMI were not significant factors for the FeNO value. Age showed borderline significance ($P = 0.050$). The absolute FVC, predicted FVC, and absolute FEV_1 were significant factors for FeNO. The multivariate linear regression analysis showed that absolute FVC and absolute FEV_1 had significantly relevant associations with FeNO levels (Table 4).

Predictive power of FeNO measurements for asthma diagnosis using a multiple regression analysis

After adjustment for pulmonary function factors (FVC and FEV_1, based on the results of Table 4), the first FeNO value measured (AUC, 0.859; 95% confidence interval [CI], 0.794–0.924; $P < 0.001$; sensitivity, 80.5%; specificity, 85.1% when cut-off value is 30.0 ppb) was not significantly inferior in asthma diagnosis to the second measured value (AUC, 0.850; 95% CI, 0.785–0.916; $P < 0.001$; sensitivity, 76.6%; specificity 85.1% when cut-off value is 29.0 ppb) (comparison of ROC curves between first FeNO value and second FeNO value, $P = 0.694$), the geometric mean of the two measurements (AUC, 0.856; 95% CI, 0.792–0.922; $P < 0.001$; sensitivity 81.8%; specificity, 83.0%) (comparison of ROC curves between first FeNO value and geometric mean FeNO value, $P = 0.923$), the larger one of the two values (AUC, 0.857; 95% CI, 0.793–0.922; $P < 0.001$; sensitivity, 79.2%; specificity, 85.1%) (comparison of ROC curves between first FeNO value and larger one, $P > 0.999$), and the smaller one of the two values (AUC, 0.859; 95% CI, 0.795–0.923; $P < 0.001$; sensitivity, 81.8%; specificity, 80.9%) (comparison of ROC curves between first FeNO value and smaller one, $P = 0.848$) (Table 5).

DISCUSSION

We demonstrated that repeated FeNO measurements during the same session are not essential for asthma diagnosis. The FeNO value was highly reproducible; the predictive value of the first FeNO measurement for asthma was not inferior to that measured the second time [15], the mean of the two values, the larger value, or the smaller value. Various institutes currently use the older protocol recommended by the 2005 ATS/ERS guidelines, which state that the FeNO level should be measured twice and the mean value should be used [7]. However, this recommendation is not supported by sufficient scientific evidence. Recently, some studies showed the excellent reproducibility and repeatability of FeNO measurements [8,9]. However, whether an asthma diagnosis can be made with only one FeNO measurement has not been studied. This study suggests that the time and effort required to measure the FeNO level repeatedly could be saved because a single FeNO measurement is sufficient to diagnose asthma.

Although we proved the excellent predictive value of a single FeNO measurement for asthma diagnosis, some patients showed a significant gap in FeNO levels between the first and second measurements. Subjects with normal-to-low FeNO values (in the bottom 75%) showed modest agreement between the FeNO values measured the first and second time. The groups with the best (in the top 25%) and worst (in the bottom 25%) lung function showed significantly higher FeNO values for the second measurement compared to the first measurement. Therefore, we need to pay attention when measuring FeNO levels in these subgroups of patients. In these patients, more than one measurement of the FeNO level can be considered to obtain the correct

value. However, it might not affect the diagnosis of asthma.

We defined lung function as a significant factor for FeNO. However, age, sex, and height were not significant factors. Several studies have demonstrated that age, sex, height, atopy, smoking status, and lung function can influence the level of FeNO [16]; however, no consensus has been reached [3-6,10,13,17,18]. We attempted to determine whether all these factors are significantly associated. This study included a relatively small number of subjects compared with previous studies. Therefore, we could not be sure that age, sex, and height were not significantly associated. We reconfirmed that lung function was negatively correlated with FeNO values, consistent with a previous article from a group in Korea [10]. Subjects with severe eosinophilic inflammation might have high levels of FeNO and poor lung function [19], which could lead to this result.

Asthma is a chronic inflammatory airway disease. Various tests have been used to diagnose and monitor asthma [20]. The classic tests involve lung function, a questionnaire, and induced sputum; FeNO and periostin have been used recently; IgE, ykl-40, CD93, and so on have gained renewed interest as potential biomarkers for asthma [21-24]. In the clinic, the FeNO level is easily measured before the performance of the lung function test. The utility of FeNO values has been widely demonstrated [25,26]; therefore, FeNO measurement will be used more extensively from now on. This study showed that repeated measurements of FeNO were unnecessary; the convenience and ease of a single FeNO measurement will enhance the utility of FeNO measurements.

There are some limitations in this study. First, this study was performed at only one institute with a small number of enrolled subjects. A further larger study will be needed to confirm the

results of this study. Second, we have a highly skilled and well-trained practitioner; this might have led to excellent reproducibility. We are unsure if a single FeNO measurement will be sufficient at other institutes without skilled trainers. Third, we should interpret the results carefully because we might include asthma patients of the non-eosinophilic type. Last, atopy which is known to be significantly associated with FeNO level could not be included for analysis, because there are many missing data.

In conclusion, a single FeNO measurement was sufficient for asthma screening in cases where the first acceptable FeNO measurement was performed using the proper method. A second measurement would be helpful in cases where the first acceptable measurement is much less than or greatly exceeds the clinician's expectation and in cases where the patient's lung function is extremely good or poor.

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Figure 1. Correlation (A) and comparison (B) of FeNO between measured at 1st and 2nd time

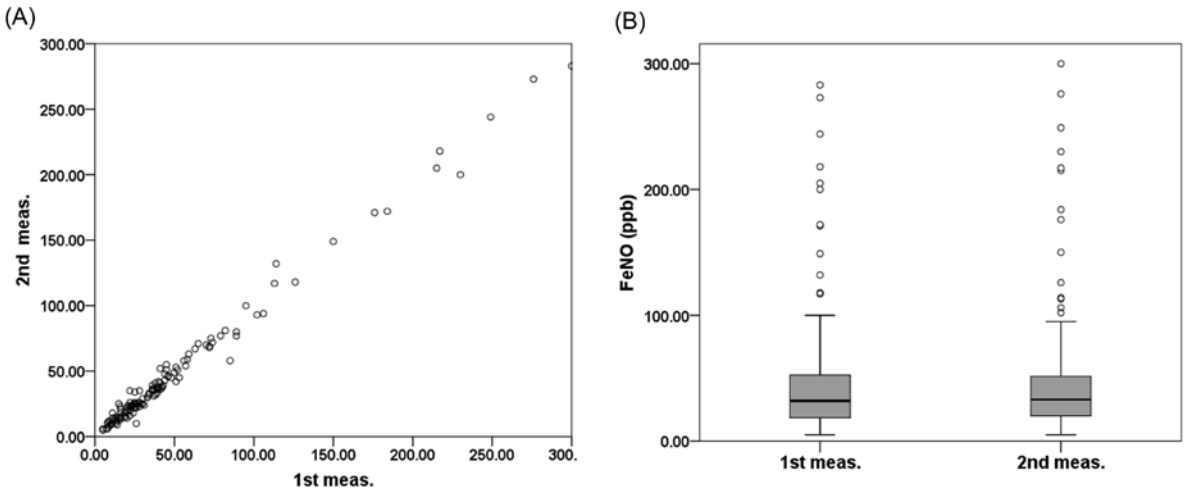

Table 1. Clinical characteristics, pulmonary function test, and geometric mean of FeNO according to group

Variables	Total (n=132)	Subjects without large gap (n = 99)	Subjects with large gap (n = 33)	*P*-value
Sex (Male)	50.0%	51.5%	45.5%	0.546
Age	42.8 ± 16.0	41.9 ± 15.2	45.5 ± 18.2	0.307
Height	165.7 ± 9.2	166.5 ± 9.4	163.1 ± 7.9	0.079
Weight	66.6 ± 13.1	66.1 ± 14.0	67.9 ± 10.1	0.535
BMI	**24.2** ± 3.7	**23.7 ± 3.5**	**25.6 ± 3.9**	**0.015**
Absolute FVC	3.8 ± 1.0	3.9 ± 1.0	3.6 ± 1.0	0.094
Predicted FVC	97.3 ± 13.0	97.9 ± 13.1	95.7 ± 12.8	0.419
Absolute FEV_1	3.0 ± 0.8	3.0 ± 0.8	2.8 ± 0.9	0.226
Predicted FEV_1	99.1 ± 16.3	99.1 ± 16.2	99.1 ± 16.8	0.998
Asthma	**59.8%**	**66.7%**	**39.4%**	**0.005**
Geometric mean of FeNO				
1st meas.	**32.5 ± 2.3**	**37.7 ± 2.4**	**20.9 ± 1.8**	**< 0.001**
2nd meas.	**33.4 ± 2.3**	**38.5 ± 2.4**	**21.8 ± 1.8**	**0.001**

BMI, body mass index; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; FeNO, fractional exhaled nitric oxide; meas., measurement

Large gap was defined as more than 17.5% difference of FeNO between measured at 1st and 2nd time

Bold presents significant factors for obtained by independent samples *t*-test.

Table 2. Reliability, correlation, and comparison of FeNO measurements

	Variables	Number of subject	Intraclass correlation		Pearson's correlation		Paired *t*-test		
			Coefficient	*P*-value	Coefficient	*P*-value	1st meas.	2nd meas.	*P*-value
Sex	Male	66	0.988	< 0.001	0.977	< 0.001	33.28	33.62	0.584
	Female	66	0.989	< 0.001	0.979	< 0.001	31.83	33.20	0.095
Age	< 65	115	0.991	< 0.001	0.983	< 0.001	32.26	32.83	0.236
	≥ 65	17	0.929	< 0.001	0.952	< 0.001	34.56	37.61	0.233
BMI	< 18.5	6	> 0.999	< 0.001	0.999	< 0.001	40.17	39.75	0.428
	18.5-23	40	0.986	< 0.001	0.973	< 0.001	28.17	29.32	0.222
	23-25	29	0.989	< 0.001	0.979	< 0.001	34.85	36.34	0.210
	>25	40	0.983	< 0.001	0.967	< 0.001	29.84	29.86	0.984
FVC	< 25% (<3.12L)	31	0.989	< 0.001	0.980	< 0.001	40.60	44.36	0.024*
	25-50% (3.12-3.71 L)	32	0.988	< 0.001	0.979	< 0.001	31.11	30.42	0.507
	20-75% (3.71-4.65 L)	30	0.988	< 0.001	0.976	< 0.001	32.59	32.66	0.944
	> 75% (>4.65 L)	31	0.995	< 0.001	0.991	< 0.001	28.79	30.74	0.004*
FEV_1	< 25% (<2.46 L)	31	0.989	< 0.001	0.979	< 0.001	48.59	52.00	0.088
	25-50% (2.46-3.00 L)	33	0.978	< 0.001	0.958	< 0.001	30.77	31.47	0.466
	20-75% (3.00-3.58 L)	29	0.989	< 0.001	0.978	< 0.001	23.97	23.60	0.642
	> 75% (>3.58 L)	31	0.995	< 0.001	0.991	< 0.001	32.50	34.34	0.014*
FeNO	**< 25% (< 18.25)**	**33**	**0.866**	**< 0.001**	**0.774**	**< 0.001**	**11.76**	**12.67**	**0.117**
	25-50% (18.25-32.00)	**34**	**0.772**	**< 0.001**	**0.715**	**< 0.001**	**24.40**	**24.74**	**0.613**
	50-75% (32.00-52.75)	**32**	**0.780**	**< 0.001**	**0.681**	**< 0.001**	**40.04**	**39.77**	**0.783**
	> 75% (> 52.75)	33	0.991	< 0.001	0.983	< 0.001	99.14	101.38	0.204
Total		132	0.989	< 0.001	0.978	< 0.001	32.55	33.40	0.094

BMI, body mass index; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; FeNO, fractional exhaled nitric oxide; meas., measurement

*P-value < 0.05 obtained by paired *t*-test

Bold presents slightly decreased reliability and correlation of FeNO between measured at 1st and 2nd time.

Table 3. Agreement rate between FeNO positivity (≥ 30 ppb) and asthma

Variables		1st meas.	2nd meas.	Numerical mean of two above	Larger one selection between two above	Smaller one selection between two above
FVC	< 25% (<3.12L)	**87.1%**	83.9%	**87.1%**	83.9%	**87.1%**
	25-50% (3.12-3.71 L)	**84.4%**	75.0%	78.1%	81.3%	78.1%
	20-75% (3.71-4.65 L)	70.0%	**73.3%**	70.0%	**73.3%**	70.0%
	> 75% (>4.65 L)	**77.4%**	**77.4%**	**77.4%**	**77.4%**	**77.4%**
FEV1	< 25% (<2.46 L)	**90.3%**	87.1%	**90.3%**	87.1%	**90.3%**
	25-50% (2.46-3.00 L)	**75.8%**	69.7%	69.7%	**75.8%**	69.7%
	20-75% (3.00-3.58 L)	**69.0%**	**69.0%**	**69.0%**	**69.0%**	**69.0%**
	> 75% (>3.58 L)	**83.9%**	**83.9%**	**83.9%**	**83.9%**	**83.9%**
FeNO	< 25% (< 18.25)	**70.0%**	**70.0%**	**70.0%**	**70.0%**	**70.0%**
	25-50% (18.25-32.00)	**70.6%**	67.6%	**70.6%**	67.6%	**70.6%**
	50-75% (32.00-52.75)	**81.3%**	78.1%	75.0%	**81.3%**	78.1%
	> 75% (> 52.75)	**97.0%**	**97.0%**	**97.0%**	**97.0%**	**97.0%**
Total		**79.5%**	78.0%	78.0%	78.8%	78.8%

FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; FeNO, fractional exhaled nitric oxide; meas., measurement
Bold presents the highest agreement rate in sub-group.

Table 4. Significant factors determining the FeNO value

BMI, body mass index; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; FeNO, fractional exhaled nitric oxide;

	Univariate analysis			Multivariate analysis		
	Coefficients	Standard error	*P*-value	Coefficients	Standard error	*P*-value
Gender	-0.045	0.147	0.763			
Age	0.009	0.005	0.050	0.003	0.006	0.637
Height	-0.004	0.008	0.596			
Weight	-0.006	0.006	0.284			
BMI	-0.021	0.021	0.311			
Absolute FVC	**-0.195**	**0.092**	**0.035**	**0.361**	**0.174**	**0.041**
Predicted FVC	-0.009	0.005	0.045	-0.001	0.007	0.846
Absolute FEV_1	**-12.740**	**5.669**	**0.026**	**-0.532**	**0.219**	**0.017**
Predicted FEV_1	< 0.001	0.006	0.996			

meas., measurement

Bold presents significant factors for FeNO measured at 1st time obtained by multivariate linear regression analysis.

Table 5. Predictive power of FeNO measurements for asthma diagnosis using a multiple regression analysis

Variables	AUC	95% CI	*P*-value	Sensitivity	Specificity
1st meas.	**0.859**	**0.794, 0.924**	**< 0.001**	**80.5%**	**85.1%**
2nd meas.	0.850	0.785, 0.916	< 0.001	76.6%	83.0%
geometric mean of two above	0.856	0.792, 0.922	< 0.001	81.8%	83.0%
Larger one selection between two above	0.857	0.793, 0.922	< 0.001	79.2%	85.1%
Smaller one selection between two above	0.859	0.795, 0.923	< 0.001	81.8%	80.9%

FeNO, fractional exhaled nitric oxide; meas., measurement; AUC,

All data are obtained by logistic regression after adjustment with absolute FVC and $FEV_{1.}$
Bold presents the best results among the variables.