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Re-evaluation of the diagnostic value of fractional exhaled nitric oxide & its impact in patients with asthma

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***Background & objectives*: The diagnostic value of fractional exhaled nitric oxide (FeNO) in patients with asthma remains controversial. This study was aimed to re-evaluate the diagnostic value of FeNO in specific groups with asthma and identify potential factors associated with FeNO.**

***Methods*: FeNO measurement and bronchial provocation test (BPT) or bronchodilator test (BDT) were performed in patients with suggestive symptoms for asthma. Correlation analysis was performed, and receiver-operating characteristic (ROC) curves and area under the curve (AUC) were calculated to evaluate the accuracy of FeNO in diagnosis.**

***Results*: A total of 265 (66.3%) patients with asthma were identified in 400 individuals suspected to have asthma from October 2014 to June 2015. Positive correlations of gender (r=0.138, *P*=0.005), atopy (r=0.598, *P*<0.001) and rhinitis (r=0.485, *P*<0.001) but negative correlations of age (r=−0.220, *P*<0.001) and the cumulative methacholine dosage with a 20 per cent decrease in forced expiratory volume in one second (r=−0.197, *P*<0.001) with FeNO were found. AUC of FeNO in whole population and patients with atopy and rhinitis was 0.728 [95% confidence interval (CI) 0.675-0.781, *P*<0.001] and 0.752 (95% CI 0.640-0.865, *P*<0.001), while the cut-offs were 23.5 and 44.5 parts per billion (ppb), respectively, rendering sensitivities, specificities, positive predictive value and negative predictive value of 79.9, 54.7, 77.9, 58.1 and 78.7, 67.9, 89.2 and 48.7 per cent, respectively. The cut-off of FeNO with specificity of 90 per cent ($FeNO_{90}$) for all patients and a sub-group of patients with atopy and rhinitis was 59.5 and 90.5 ppb, respectively, while $FeNO_{90}$ decreased by 12 ppb with every 10 years.**

***Interpretation & conclusions*: Our findings show that the diagnostic value of FeNO varies in different groups of patients with asthma, thus, the cut-off point should be adjusted in different asthmatic sub-populations. A cut-off point of FeNO with a specificity >90 per cent could decrease the false-positive rate.**

Key words Age - asthma - atopy - diagnosis - fractional exhaled nitric oxide - rhinitis

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Asthma is a common chronic airway disease with an increasing prevalence of 1-18 per cent in different countries and populations[1,2]. It has been widely acknowledged that chronic airway inflammation and hyper-responsiveness are essential characteristics underlying pathogenesis of asthma, in which many cells and cellular elements induced by the interaction of genetic backgrounds and environment exposures play roles[1,3,4].

Bronchial provocation test (BPT) and bronchodilator reversibility test (BDT) are the most commonly used methods in spirometry, of which BPT represents airway hyper-responsiveness while BDT evaluates the extent of airflow reversibility. However, these cannot directly reflect the airway inflammation, and are complicated and time-consuming procedures. Therefore, studies were focused on the novel biomarkers in the diagnosis and assessment of asthma, especially nitric oxide (NO). In 1991, Gustafsson *et al* reported for the first time that endogenous NO was present in the exhaled air[5], and afterwards, more studies demonstrated that the level of NO was elevated in the expired air of asthmatics[6], which made the NO detection in the exhaled air possible and feasible in the patients with asthma. Fractional exhaled NO (FeNO) is a non-invasive measure of airway inflammation, which has been recommended to differentiate asthma airway inflammation phenotypes as well as predict treatment responses to inhaled corticosteroids (ICS) and risk for exacerbation and recurrence[1]. For example, The American Thoracic Society (ATS) guidelines divided FeNO levels into three sub-groups, that is <25 parts per billion (ppb), 25-50 ppb and >50 ppb, in adults to identify eosinophilic airway inflammation[7].

In a systematic review, 26 studies with 4518 participants were included to investigate the diagnostic accuracy of FeNO and it was found that there appeared to be a fair accuracy of FeNO for making the diagnosis of asthma[8]. However, the diagnostic value of FeNO in patients with asthma remained controversial[9,10], which also resulted in the recommendation by ATS that FeNO could not independently serve as a diagnostic tool for asthma[7]. Asthma is a heterogeneous disease, and many factors are known to be associated with FeNO including airway inflammation subtypes, age, obesity, races, as well as comorbidities, such as rhinitis and atopy[11-14]. Petsky *et al*[15,16] analysed seven studies of 1700 participants to evaluate the efficacy of tailoring asthma interventions based on FeNO in comparison to not using FeNO, and found that it might be beneficial in a subset of patients with frequent exacerbations both in children and adults. Therefore, we suspected that the diagnostic value of FeNO may be different in specific subset of asthmatics. Hence, this study was conducted to identify the potential factors associated with FeNO and to re-evaluate the diagnostic value of FeNO in specific groups with asthma.

Material & Methods

Outpatients from Respiratory department, who visited hospital for the first time for the evaluation of suspected asthma, were consecutively recruited from October 2014 to June 2015 in West China Hospital, Sichuan University, Sichuan, PR China. The study protocol was approved by the research ethics committee, and all patients provided written informed consent.

The sample size was calculated by the formula $[n=(Z_{\alpha/2})^2 p(1-p)/d^2]$, where n was number of patients needed in the study, $\alpha=0.05$, $Z_{\alpha/2}$ was inserted by 1.96, p was sensitivity or specificity and d was permissible error[17]. One hundred individuals were enrolled in the pilot study; the sensitivity and specificity of FeNO in diagnosing asthma were 52.4 and 81.1 per cent, respectively, at a cut-off of 42.5 ppb determined by receiver-operating characteristic (ROC) curves when Youden's index reached maximum. Hence, according to the formula, at least 149 patients were needed in the experiment group and 92 individuals in the control group.

Patients were excluded when they presented with one of the following: (*i*) upper respiratory tract infection during four weeks before visit; (*ii*) severe cardiovascular diseases such as fatal arrhythmia and myocardial infarction; (*iii*) other severe pulmonary diseases with an influence in lung function including but not limited to severe pneumonia, bronchiectasis, emphysema, pneumothorax, pulmonary fibrosis, allergic bronchopulmonary aspergillosis, tuberculosis and lung cancer; or (*iv*) refusing FeNO, BPT or BDT measurements.

Fractional exhaled nitric oxide (FeNO) detection and BPT/BDT procedures: FeNO detection was performed in all enrolled patients, while BPT or BDT was conducted based on the baseline forced expiratory volume in one second (FEV_1). All measurements were recommended by the corresponding guidelines[18-20]. Because spirometric manoeuvres have been shown to transiently reduce exhaled NO levels, NO analysis was performed before spirometry[18].

FeNO concentration was measured by chemoluminescence using NO monitor (NIOX MINO; Aerocrine AB, Solna, Sweden) at an expiratory flow rate of 50 ml/sec, which was performed at least twice until at least two NO plateau values were obtained within 10 per cent of each other and expressed as ppb. Spirometry was performed by JAEGER spirometer (Master Screen Spirometer, Jaeger Corp, Germany) and was performed more than three times until three acceptable spirograms have been obtained when the two largest values of fixed vital capacity (FVC)/FEV_1 were within 0.150 l of each other[20]. If FEV_1% of predicted was ≥70 per cent, BPT was performed with methacholine, and the cumulative methacholine dosage with a 20 per cent decrease in FEV_1 (PD_{20}) was recorded; while if FEV_1% of predicted was <70 per cent, BDT was conducted with an inhalation of 400 mg salbutamol, and a positive BDT was rendered as an increase in FEV_1 of >12 per cent and >200 ml from baseline.

Definition of asthma, atopy and rhinitis: The diagnostic criteria of asthma included: (*i*) a history of recurrent wheeze, shortness of breath, chest tightness, and cough ≥3 months; (*ii*) positive BPT or BDT; and (*iii*) obvious alleviation of symptoms after treatment with ICS or plus long-acting $beta_2$ agonist for a month[21]. Atopy was defined as a positive skin prick test response to at least one of the following 10 allergens including house dust mite, *Dermatophagoides farinae*, cat and dog fur, cockroach, ragweed pollen, humulus pollen, Artemisia annua pollen, *Cladosporium cladosporioides* and *Alternaria alternata*. Rhinitis is defined as an inflammation of the lining of the nose and is characterized by nasal symptoms including anterior or posterior rhinorrhoea, sneezing, nasal blockage and/or itching of the nose. These symptoms occur during two or more consecutive days for more than one hour on most days[22]. Hence, in our study, rhinitis was defined when the patients presented with two or more of the following symptoms with a duration more than one hour per day: rhinorrhoea, sneezing, nasal blockage and nasal itching.

Statistical analysis: Student's *t* test was used to compare mean values between two independent groups when the study variable was a normal variate and the variances between the groups were homogenous, while rank sum test was used when variances were heteroscedastic. Chi-square test was applied to test dichotomous variables. Pearson's correlation analysis or Spearman's rank correlation analysis was used for correlation analysis[23], and partial correlation analysis was conducted to adjust confounders for FeNO. Based on the identified factors, the patients were divided into groups with different comorbidities and ages. About rhinitis and atopy, patients were divided into eight groups according to three-way classification (asthma×rhinitis×atopy). Then, Welch test was applied to compare FeNO levels in different patient groups when values were heterogeneous variances. ROC curves were plotted between (1 - specificity) versus sensitivity for graphical illustration of diagnostic value[24]. Cut-off point was calculated when Youden's index reached maximum (FeNOmax) or specificity exceeded 90 per cent ($FeNO_{90}$) as well as the corresponding sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) to evaluate the accuracy of FeNO in determining asthma[25]. Data analysis was performed by the SPSS 21.0 software (SPSS Inc, Chicago, IL, USA).

Results

A total of 651 patients were screened, and eventually 400 eligible patients were enrolled in the final analysis; the male/female ratio was 132/268, aged from 18 to 72 yr. Among the 251 excluded patients, 189 refused BPT/BDT and 62 refused FeNO detection.

Demographic characteristics: There were 265 (BPT-129 and BDT-136) patients with asthma among 400 eligible patients. No significant difference was observed between asthmatics and non-asthmatic patients in respect of age, gender and body mass index (BMI) while FeNO (ppb), log_{10} FeNO, atopy (%), and rhinitis (%) were observed to be significantly (P<0.05) higher in asthmatic patients than non-asthmatics (Table I).

Factors associated with FeNO: Correlation analysis between potential factors and FeNO showed a positive correlation in gender (r=0.138, P=0.005), atopy (r=0.598, P<0.001) and rhinitis (r=0.485, P<0.001), while a negative correlation in age (r=−0.220, P<0.001) and PD_{20} (r=−0.197, P<0.001). No correlation was observed between BMI, FEV_1, FEV_1/FVC or change of FEV_1% predicted. Although the overall FEV_1% predicted was not significantly associated with FeNO, a significant correlation was observed after FEV_1% predicted was divided into mild (r=−0.156, P=0.023) and moderate-to-severe (r=0.301, P<0.001) obstructive airflow limitation with a reference cut-off point of 70 per cent. To eliminate the interference

of confounders, partial correlation analysis showed that rhinitis (r=0.279, *P*=0.005) and atopy (r=0.435, *P*=0.001) were positively correlated with FeNO, by including sex, age, BMI and atopy or rhinitis as covariates.

FeNO levels in different patient groups: On the basis of significant correlation of FeNO with rhinitis and atopy, the patients were divided into different groups to depict the FeNO levels. There was a significant difference between eight groups in general (F=34.07, *P*=0.001), and high FeNO level of 76.9±35.9 ppb was found in asthma with atopy and rhinitis, which was significantly higher than other asthmatic and non-asthmatic patients, and FeNO level in asthma with atopy group was second with 47.1±19.7 ppb (Table II). The patients were also divided patients into five groups by age with an interval of 10 yr, and the results showed a significant decreasing trend of FeNO with increasing age (Fig. 1).

Diagnostic value of FeNO in different patient groups: The area under the curve (AUC) of FeNO in relation to the diagnosis of asthma was 0.728 [95% confidence interval (CI) 0.675-0.781, *P*<0.001] for the 400 patients. The highest sum of sensitivity (79.9%) and specificity (54.7%) was achieved at a cut-off point of 23.5 ppb (FeNOmax) with an accuracy of 71.5 per cent and diagnostic odds ratio (OR) of 4.88 (95% CI 2.016-11.807), having a PPV of 77.9 per cent and NPV of 58.1 per cent (Fig. 2A and Table III).

The diagnostic value of FeNO in patients with atopy and rhinitis was higher than patients without atopy and rhinitis (AUC=0.752 vs. AUC=0.693) and had higher sensitivity and specificity (Fig. 2B, C and Table III). On the other hand, when the cut-off point was 23.5 ppb, it had very high accuracy (NPV=100%) to figure out non-asthmatic in patients with atopy and rhinitis (data not shown). The patients were also classified into mild (FEV_1% predicted ≥70%) and moderate-to-severe (FEV_1% predicted <70%) obstructive airflow limitation, and the results showed a higher diagnostic value of FeNO to identify asthma in patients with mild obstructive airflow limitation than moderate-to-severe airflow limitation (AUC=0.801 vs. AUC=0.628) (Fig. 3 and Table III) with a FeNOmax of 23.5 and 45.5 ppb, respectively.

Table I. Baseline characteristics of enrolled patients (n=400)

Characteristics	Asthma (n=265)	Non-asthma (n=135)	*P*
Age (yr)	44.4±12.3	43.4±10.9	0.450
Sex (male/female)	96/169	36/99	0.055
Height (cm)	159.0±8.2	157.3±7.6	0.055
Body weight (kg)	59.5±13.8	58.6±10.3	0.503
BMI (kg/m^2)	23.5±4.9	23.6±3.3	0.838
FeNO (ppb)	50.9±33.9	29.1±24.7	0.001
Log10 FeNO	1.61±0.31	1.33±0.32	0.001
Atopy (%)	164 (61.9)	39 (28.9)	0.001
Rhinitis (%)	161 (60.7)	56 (41.8)	0.031

Continuous data were displayed as mean±SD; dichotomous data were displayed in case and percentage. BMI, body mass index; FeNO, fractional exhaled nitric oxide; SD, standard deviation

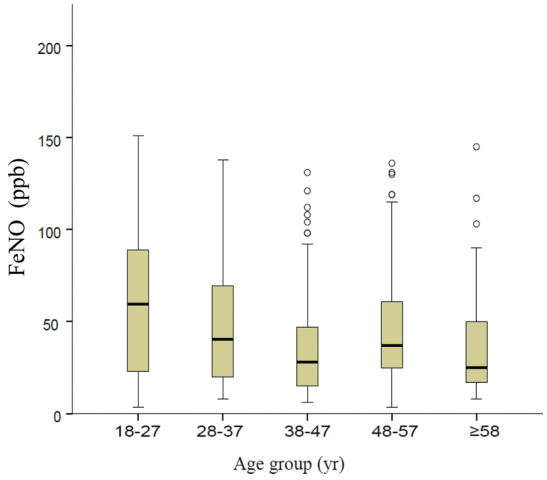

Fig. 1. FeNO levels in different age categories. FeNO had a significant decreasing trend with increasing age. The average FeNO level in different age group were 64.6 ppb, 49.1 ppb, 36.2 ppb, 43.8 ppb and 37.3 ppb, respectively. There were 6, 4, and 3 outliers in age group 38-47, 48-57, and ≥58, respectively. FeNO, fractional exhaled nitric oxide.

Table II. Fractional exhaled nitric oxide levels (ppb) in different asthma and non-asthma sub-groups

Sub-groups	Atopy + rhinitis	Atopy + non-rhinitis	Non-atopy + rhinitis	Non-atopy + non-rhinitis
Asthma (n=265)	76.9±35.9[§] (n=94)	47.1±19.7 (n=70)	41.4±30.5 (n=19)	26.7±17.7 (n=82)
Non-asthma (n=135)	46.5±35.1 (n=28)	42.1±20.1 (n=11)	46.3±24.5 (n=8)	20.4±15.4 (n=88)

Data were reported as mean±SD; *F*=34.07, *P*<0.001; [§]Comparison between group of asthma + atopy + rhinitis and other sub-groups, *P*<0.05

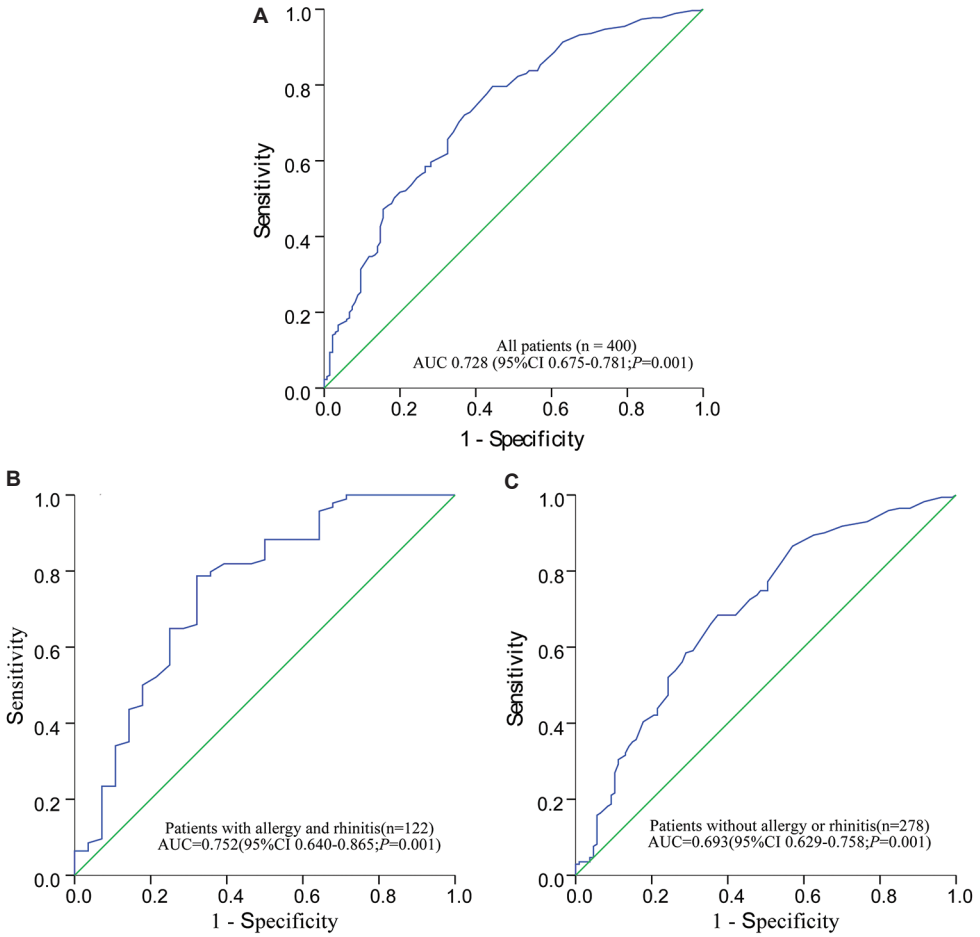

Fig. 2. ROC curve of FeNO in different sub-populations of patients. (**A**) ROC curve of FeNO in all patients (n=400). AUC of FeNO in identifying asthma in this patient group was 0.728 (95% CI 0.675-0.781, *P*<0.001); (**B**) ROC curve of FeNO in patients with allergy and rhinitis (n=122). AUC of FeNO in identifying asthma in this patient group was 0.752 (95% CI 0.640-0.865, *P*<0.001); (**C**) ROC curve of FeNO in patients without allergy or rhinitis (n=278). AUC of FeNO in identifying asthma in this patient group was 0.693 (95% CI 0.629-0.758, *P*<0.001). AUC, area under the curve; FeNO, fractional exhaled nitric oxide; ROC curve, receiver-operating characteristic curve; CI, confidence interval.

Table III. Diagnostic value of cut-off point of fractional exhaled nitric oxide when Youden's Index reached maximum in different patient sub-groups

Sub-groups	AUC	$FeNO_{max}$ (ppb)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
All patients	0.728	23.5	79.9	54.7	77.9	58.1
Patients with atopy and rhinitis	0.752	44.5	78.7	67.9	89.2	48.7
Patients without atopy or rhinitis	0.693	23.5	68.4	62.6	74.5	55.4
Patients with FEV_1% predicted ≥70%	0.801	23.5	80.9	65.8	80.3	66.7
Patients with FEV_1% predicted <70%	0.628	45.5	44.1	78.9	83.3	37.2
Patients aged 18-27	0.744	13.0	100	60.0	88.6	100
Patients aged 28-37	0.757	24.5	86.5	59.3	74.4	72.7
Patients aged 38-47	0.711	23.5	77.4	60.8	76.5	62.0
Patients aged 48-57	0.685	47.5	39.5	90.0	90.9	37.0
Patients aged >58	0.670	35.5	52.5	94.1	95.5	45.7

All of the 400 patients finally enrolled in the study. AUC, area under the curve; $FeNO_{max}$, Cut-off point of fractional exhaled nitric oxide when Youden's Index reached maximum; NPV, negative predictive value; PPV, positive predictive value; FEV_1%, forced expiratory volume in one second

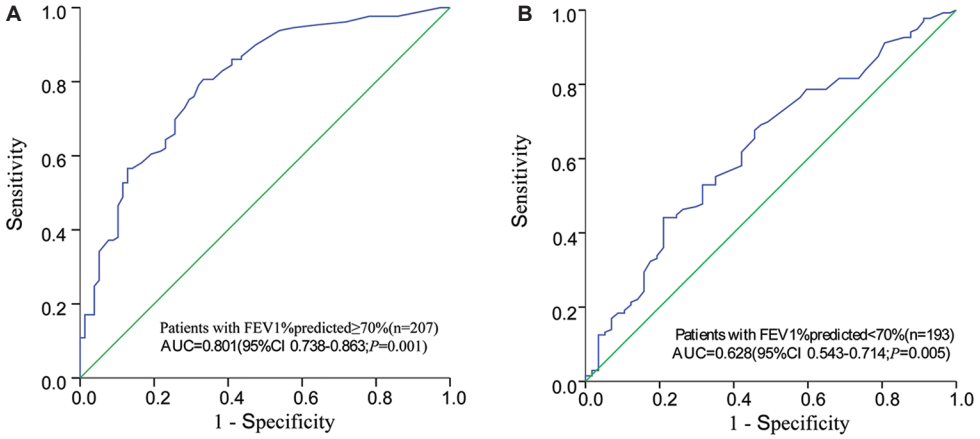

Fig. 3. (**A**) ROC curve of FeNO in patients with FEV1% predicted ≥70 or 70 per cent. Curve of FeNO in patients with FEV_1% predicted ≥70 per cent (n=207). AUC of FeNO in identifying asthma in this patient group was 0.801 (95% confidence interval 0.738-0.863, *P*<0.001); (**B**) ROC curve of FeNO in patients with FEV_1% predicted <70 per cent (n=193). AUC of FeNO in identifying asthma in this patient group was 0.628 (95% CI 0.543-0.714, *P*=0.005). AUC, area under the curve; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in one second; ROC curve, receiver-operating characteristic curve; CI, confidence interval.

In all age groups, it was found that a cut-off point of 23.5 ppb could effectively identify the candidate patients with risk of asthma due to the relatively high sensitivity ranging from 65.0 to 89.2 per cent but had less power to make a diagnosis of asthma for the relatively low specificity between 40.0 and 60.8 per cent (data not shown). However, the sensitivity and specificity of FeNO in identifying asthma were both improved when a specific FeNOmax was established in every different age group (Table III), and there was higher sensitivity among young people while higher specificity among the elderly.

For a diagnostic specificity >90 per cent, the corresponding cut-off points of FeNO ($FeNO_{90}$) were calculated for different patient groups. $FeNO_{90}$ was significantly higher than FeNOmax in all sub-groups with ideal specificity and PPV. In patients with different age groups, a decreasing trend of $FeNO_{90}$ was found by about 12 ppb every 10 yr (Table IV).

Discussion

FeNO is a novel biomarker for airway eosinophilic inflammation. However, the accurate diagnostic value of FeNO in asthma has not reached a consensus due to the various cut-off points and outcomes from different studies[9,10]. Woo *et al*[9] investigated 245 children with

Table IV. Diagnostic value of cut-off point of fractional exhaled nitric oxide when specificity exceeded 90% in different patient sub-groups

Sub-groups	AUC	$FeNO_{90}$ (ppb)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
All patients	0.728	59.5	32.7	90.0	86.0	40.0
Patients with allergy and rhinitis	0.752	90.5	34.0	92.6	94.1	28.7
Patients without allergy or rhinitis	0.693	54.5	20.6	90.7	77.8	41.8
Patients with FEV_1% predicted ≥70%	0.801	48.0	46.5	90.0	88.2	50.4
Patients with FEV_1% predicted <70%	0.628	76.5	19.1	90.0	71.9	31.7
Patients aged 18-27	0.744	84.5	35.4	90.0	91.7	31.0
Patients aged 28-37	0.757	72.0	35.1	92.6	86.7	51.0
Patients aged 38-47	0.711	59.5	23.8	94.1	87.0	42.9
Patients aged 48-57	0.685	47.5	39.5	90.0	90.9	37.0
Patients aged >58	0.670	35.5	52.5	94.1	95.5	45.7

All 400 patients finally enrolled in the study. AUC, area under the curve; $FeNO_{90}$, cut-off point of fractional exhaled nitric oxide when specificity exceeded 90%; NPV, negative predictive value; PPV, positive predictive value; FEV_1%, forced expiratory volume in one second

symptoms suggestive of asthma using FeNO; the sensitivity, specificity, PPV and NPV of were 56.9, 87.2, 90.5, and 48.6 per cent at the best cut-off value of 22 ppb, which was further demonstrated by other studies but with different cut-off point of FeNO and diverse sensitivity and specificity[10,26]. A previous study in Chinese patients with asthma also yielded a high sensitivity (79.2%) and specificity (94.3%) at 36.5 ppb[27].

As shown in our study, a large number of factors may be associated with FeNO, such as age, gender, rhinitis, atopy[11-14], PD_{20} and even FEV_1%. In our study, atopy (r=0.598) and rhinitis (r=0.485) were most relevant to FeNO. Moreover, asthmatics with allergy and rhinitis had higher diagnostic value than asthmatics without atopy and rhinitis. In our study, FeNOmax at 23.5 ppb in the all patients had a low specificity (54.7%) and NPV (58.1%), indicating a low accuracy of diagnosis. However, it significantly improved in patients with atopy and rhinitis with sensitivity and NPV reaching 100 per cent, which indicated a critical clinical implication that asthma could be excluded if FeNOmax <23.5 ppb was detected in patients with atopy and rhinitis. Our study also showed that the diagnostic value of FeNO was higher in patients undergoing BPT than BDT; the different diagnostic value and cut-off points between these two groups indicated that adaption of so-called gold standard with BPT and BDT may also influence the diagnosis value of FeNO, especially underestimating the value of FeNO by BDT. It was reported that BPT was indirectly associated with airway inflammation while BDT assessed airflow reversibility, and FeNO was reported to be associated with airway inflammation[28]; thus, a close association between FeNO and BPT rather than BDT in our study could be justified. Compared to BPT, FeNO detection is simpler, less time-consuming and easier to cooperate and complete; hence, for such symptomatic patients without airway reversibility, FeNO may be useful for diagnosis. Our results showed that age was negatively correlated with FeNO, and FeNO had a significant decreasing trend with increasing age. To found the diagnostic value of FeNO in specific age group, the patients were divided into different age groups with an interval of 10 yr, and the result showed that sensitivity and specificity of FeNO in identifying asthma were both improved when a specific FeNOmax was established in each age group.

In 2014, the National Institute for Health and Care Excellence[29] reviewed identified studies and found that estimates of specificity consistently had a smaller range and higher values than estimates of sensitivity reported, suggesting that FeNO testing appeared to have a higher specificity than sensitivity. A systematic review including 26 studies with 4518 participants showed that in diagnosis of asthma FeNO had higher overall specificity (0.82) than sensitivity (0.65), which indicated a higher diagnostic potential for ruling-in than for ruling-out the diagnosis of asthma[9]. A rule-in test implies that patients whose test is positive are assumed to have asthma and those negative may have further tests for asthma. With the aim of improving diagnostic specificity, the cut-off point of FeNO ($FeNO_{90}$) was calculated with specificity >90 per cent. In all patients with mixed clinical conditions, the $FeNO_{90}$ was 59.5 ppb, indicating a relatively high possibility of asthma (specificity=90%, PPV=86%) when FeNO level was >59.5 ppb. However, FeNOmax may not be sufficient and optimal in clinical setting, and a range of FeNO value established on the basis of sensitivity and specificity may improve the diagnostic value and reduce false-positive and false-negative rate. Schneider *et al*[26] suggested the lower and upper FeNO limit of ≤12 ppb and >46 ppb. Future studies need to be done to verify this hypothesis.

This study had limitations. As a diagnostic value study of FeNO, no blood or induced sputum biomarkers were collected, leading to the inability to analyse correlation of eosinophils and FeNO. Smoking is a significant confounder for the interpretation of FeNO value, but we did not collect information about the smoking status of patients. In our study, the FeNO values had relatively high variability because of individual difference and small sample size; maybe, the use of $\log_{10}$ FeNO in place of net FeNO values in the diagnosis of asthma can reduce the variability and solve this problem. The Welch test also suggests log transformation of FeNO observations, but our study did not carry out log transformation analysis.

Since the diagnostic value of FeNO varies among asthmatic patients with different clinical characteristics, an independent cut-off point of FeNO calculated for a specific clinical condition could improve the value of FeNO in diagnosing asthma. FeNO displays a higher diagnostic value in patients with mild obstructive airflow limitation or with comorbidities of atopy and rhinitis, and a cut-off point of FeNO with a specificity >90 per cent could decrease the false-positive rate.

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***Conflicts of Interest*:** None.

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