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Diagnostic value of FeNO and MMEF for predicting cough variant asthma in chronic cough patients with or without allergic rhinitis

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ABSTRACT

Objective: To evaluate the diagnostic value of fractional exhaled nitric oxide (FeNO) and maximum mid-expiratory flow (MMEF) for differentiating cough variant asthma (CVA) from chronic cough in patients with or without allergic rhinitis.

Methods: In total, 328 patients with chronic cough who underwent spirometry and FeNO testing were consecutively included in the retrospective analysis. Patients were divided into the CVA ($n = 125$) or NCVA ($n = 203$) groups according to the diagnostic criteria of CVA. Receiver operating characteristic (ROC) curves were established to assess the diagnostic efficiency and optimal cutoff points of FeNO and MMEF for the prediction of CVA.

Results: The optimal cutoff values of FeNO and MMEF to discriminate CVA from chronic cough were 24.5 ppb (AUC, 0.765; sensitivity, 69.60%; specificity 72.91%; PPV, 61.27%; NPV, 79.57%) and 66.2% (AUC, 0.771; sensitivity, 67.20%; specificity 78.33%; PPV, 65.63%; NPV, 79.50%). The optimal cutoff values of combining FeNO with MMEF to discriminate CVA from chronic cough were >22 ppb for FeNO and $<62.6\%$ for MMEF (AUC, 0.877). In patients with and without allergic rhinitis, the optimal cutoff point of FeNO to discriminate CVA from chronic cough was 24.5 ppb (AUC, 0.820) and 33.5 ppb (AUC, 0.707), respectively.

Conclusions: FeNO and MMEF might have greater value as negative parameters for differentiating CVA from chronic cough. Combining FeNO and MMEF provided a significantly better prediction than either alone. The diagnostic accuracy of FeNO for predicting CVA in chronic cough patients with allergic rhinitis was higher than in chronic cough patients without allergic rhinitis.

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Introduction

Cough is a common symptom in outpatients in the respiratory medicine department and dramatically influences patients' daily lives. It can be classified into three categories based on its duration: acute cough (<3 weeks), subacute cough (3–8 weeks) and chronic cough (>8 weeks) (1). Cough variant asthma (CVA) is a specific form of asthma that solely presents with coughing (2). In China, more than 30% of patients came to the respiratory consulting room for chronic cough, and CVA is usually the major cause (3).

A bronchial provocation test can cause airway constriction by chemical, physical or biological provocation so that bronchial hyperresponsiveness (BHR) can be judged by measuring the change in pulmonary function before and after the provocation; this is of great value

in diagnosing or excluding CVA. However, the test is time-consuming and requires specialized equipment and professional staff. Moreover, they have a high risk of inducing severe bronchospasm, and it is difficult to popularize their use in primary hospitals. All these factors lead to the misdiagnosis and missed diagnosis of CVA. Studies have shown that approximately 80.82% of chronic cough patients were misdiagnosed with chronic bronchitis or laryngitis, and approximately 91.58% of chronic cough patients used antibiotics (4). It is essential to find an easy and quick examination method to diagnose the pathogenesis of cough earlier.

Nitric oxide (NO), catalyzed by the inducible nitric oxide synthase (iNOS) in airway epithelial cells, is produced by the conversion of L-arginine (5). Therefore, the fractional exhaled nitric oxide (FeNO) is associated with Th2 cell-mediated airway inflammation. Recent

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studies have demonstrated that FeNO is a biomarker of airway inflammation, has a significant correlation with induced sputum eosinophilia and plays an important role in the etiology of chronic cough (6–10). Furthermore, a meta-analysis suggested that FeNO has moderate diagnostic value for predicting CVA in patients with chronic cough, with an AUC of 0.87, a diagnostic specificity of 85% and a sensitivity of 72% (11).

Asthma is initially considered a chronic inflammatory disease predominantly involving the large airways. However, pathologists have found that in asthma patients, inflammation of the peripheral airways is more severe than that of the central airways (12). Perez et al (13) demonstrated that small airway obstruction could be found in asthmatic patients with normal forced expiratory volume in 1 s (FEV₁) and FEV₁/FVC. The maximal mid-expiratory flow (MMEF), defined as the mean forced expiratory flows at 25–75% of the forced vital capacity (FVC), reflects the functional status of the small airways. MMEF promises to be a better indicator of BHR and eosinophilic inflammation than FEV₁, which is important for the diagnosis of asthma (14).

Allergic rhinitis (AR) is a noninfectious inflammatory disease of the nasal mucosa mediated by immunoglobulin E (IgE) after exposure to allergens. It is closely related to asthma, and the incidence of asthma complicated with AR is as high as 60–80%. Because allergic rhinitis has an effect on FeNO levels (15), our study was conducted to evaluate the role of FeNO and MMEF in the diagnosis of CVA in patients with chronic cough with or without allergic rhinitis.

Materials and methods

Subjects

We retrospectively collected information from consecutive patients with chronic cough who underwent FeNO and spirometry tests at Zhujiang Hospital of Southern Medical University from August 2017 to July 2018. The inclusive criteria were as follows: (1) 18–75 years old; (2) cough as the sole or predominant symptom lasting for at least 8 weeks, with no radiographic evidence of lung diseases; (3) no treatment with corticosteroids within the past 4 weeks; and (4) no fever, blood-stained sputum or active respiratory infection.

According to current international or national clinical guidelines (1, 3), the criteria for defining CVA were (1) cough as the sole or predominant symptom; (2) demonstration of BHR and/or variable airway

obstruction; and (3) a good treatment response to asthma therapy (bronchodilators and glucocorticosteroids). Chronic cough except CVA was diagnosed as Cough variant asthma (NCVA). The criterion for defining allergic rhinitis (AR) was the combination of history, allergy diagnosis such as skin prick tests (SPTs) and allergen specific IgE in serum to confirm the correlation between the characteristic symptoms, such as rhinorrhea, nasal obstruction, sneezing, nasal itch, and potential allergens (16). In this study, the provocative dose of methacholine causing a 20% fall in FEV₁ (PD₂₀) was adopted as the marker for BHR. BHR was defined as a PD₂₀ at less than 2.504 mg. When the patient inhaled salbutamol 400 µg, the FEV₁ increased by more than 12% and the absolute value increased by more than 200 ml after 15 min, or the daytime variability rate of peak expiratory flow (PEF) of the patient was more than 20%, indicating the existence of variable airway obstruction.

This study was approved by the ethics committee of Zhujiang Hospital of Southern Medical University (2019-KY-044-01). The need for individual consent was waived by the committee due to the retrospective nature of the study.

FeNO

FeNO was performed using a NIOX MINO (Aerocrine, Sweden) portable instrument at a constant flow rate of 50 ml/s and was performed in accordance with the ATS/ERS recommendations (17). Before the test, subjects were confirmed as not having therapy which might affect the results.

Spirometry

Spirometry was performed using the Jaeger Masterscreen device (Jaeger GmbH, Wurzburg, Germany) according to the recommendation of American Thoracic Society (ATS)/European Respiratory Society (ERS) (18).

Statistical analysis

The normality of the distributions of all continuous variables was tested using the Kolmogorov-Smirnov method. Normally distributed variables are described as the mean (SD), whereas non-normally distributed variables are described as the median (range). Comparisons between parameters of CVA and NCVA were performed using independent sample t-test or Mann-Whitney U test based on the data distribution normality. Enumeration variables are expressed as

Table 1. Comparison the characteristics of CVA and NCVA ($N = 328$).

Parameter	CVA($n = 125$)	NCVA($n = 203$)	p
Age, year	43(16-78)	38 (17-79)	0.224
Male/female, n	47/78	98/105	0.059
Height, cm	160(142-184)	162(140-190)	0.084
Weight, kg	61(39-96)	60(39-98)	0.476
Rhinitis, n [%]	54 [43.2]	60 [29.6]	0.012
Smoking history, n [%]	40 [32.0]	68 [33.5]	0.779
FeNO, ppb	36(5-188)	16(5-121)	0.000
FVC, % predicted	103.8 (14.1)	104.0 (14.0)	0.886
FEV1, % predicted	95.4(12.4)	101.9(13.3)	0.000
FEV1/FVC, %	76.4(63.1-95.9)	82.3(65.2-98.6)	0.000
PEF, % predicted	89.0(14.5)	95.7(15.2)	0.000
MMEF, % predicted	58.6(24.9-121.1)	81.6(36.6-155.1)	0.000
MEF75, % predicted	85.3(16.7)	99.1(17.8)	0.000
MEF50, % predicted	64.2(27.8-130.7)	89.6(39.1-168.6)	0.000
MEF25, % predicted	49.8(17.8-137.3)	70.8(28.9-161)	0.000

Data are expressed as mean (SD) or median (range), unless indicated otherwise.

CVA, cough variant asthma; NCVA, non-cough variant asthma; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; PEF, peak expiratory flow; MMEF, forced expiratory flow between 25 and 75%; MEF75, forced expiratory flow at 75% of the FVC; MEF50, forced expiratory flow at 50% of the FVC; MEF25, forced expiratory flow at 25% of the FVC.

Table 2. Comparison of FeNO values between CVA and NCVA.

	CVA($n = 125$)	NCVA($n = 203$)	p
All patients	36 (5-188)	16 (5-121)	<0.001
·Rhinitis	55($n = 54$) (11-188)	23($n = 60$) (5-121)	<0.001
·Non-Rhinitis	25($n = 71$) (5-129)	14($n = 143$) (5-50)	<0.001

Data are expressed as mean (SD) or median (range), unless indicated otherwise. FeNO, fractional exhaled nitric oxide; ppb, parts per billion; CVA, cough variant asthma; NCVA, non-cough variant asthma.

numbers (percentages) and were analyzed using the chi-square test. The diagnostic values of single or combined parameters for CVA were evaluated using receiver operating characteristic (ROC) curves. Differences in areas under the curves (AUCs) between rhinitis and non-rhinitis subjects were assessed by the DeLong test. A two-sided p values < 0.05 was considered statistically significant. ROC curve analysis was performed with MedCalc Version 18.2.1 (MedCalc, Mariakerke, Belgium). Other statistical analysis were performed using IBM SPSS Statistics 19.0 (IBM Corporation, Armonk, NY, USA).

Results

Clinical data from 328 patients matched with the inclusion criteria were included. The bronchial provocation test was performed in 317 patients, 117 of whom were positive. Eleven subjects were tested with bronchodilation tests, and 8 of them were positive. Therefore, 125 (38.1%) subjects were diagnosed with CVA, and 203 (61.9%) patients were diagnosed with NCVA. A comparison of the clinical characteristics between the CVA and NCVA groups, including smoking history, spirometry and FeNO, is shown in Table 1. As illustrated in the table1, FeNO levels were significantly higher in patients with CVA ($P < 0.001$). The proportion of rhinitis subjects was 43.2% among

those with CVA, which was higher than the proportion of the NCVA group ($P < 0.05$). In contrast, the results of spirometry (FEV1, FEV1/FVC, PEF, MMEF, MEF75, MEF50 and MEF25) were significantly lower in the CVA group than in compared with the NCVA group ($P < 0.001$). No significant difference was found in other parameters.

The FeNO level of the CVA group [36 (5–188) ppb] was significantly higher than that of the NCVA group [16 (5–121) ppb] ($p < 0.001$) according to the Mann-Whitney U test (Table 2). The proportion of patients with allergic rhinitis was significantly higher in the CVA group than in the NCVA group ($P < 0.001$), and the level of FeNO was higher in asthma patients with allergic rhinitis than in those without allergic rhinitis. In addition, we further performed the Mann-Whitney U test to evaluate the effects of allergic rhinitis (Table 2). The results showed that FeNO levels were significantly higher in the CVA group than in the NCVA group in patients both with and without allergic rhinitis ($P < 0.001$).

Significant differences in the values of parameters (FeNO, FEV1, FEV1/FVC, PEF, MMEF, MEF75, MEF50, and MEF25) were found between the CVA and NCVA groups, therefore, these may be potential diagnostic indicators for differentiating CVA from chronic cough. ROC curves were constructed to evaluate the value of these parameters for distinguishing CVA from NCVA. The AUCs and optimal cutoff values were calculated (Table 3). As shown in Table 3, the largest AUCs for diagnosing CVA were those of FeNO (AUC, 0.765), MMEF (AUC, 0.771) and MEF50 (AUC, 0.780), for which the optimal cut-off points were 24.50 ppb, 66.20% and 73.70%, respectively.

Table 3. Optimal cutoff values for the prediction of CVA.

Parameter	Cutoff	AUC(95%CI)	Sensitivity	Specificity	PPV(%)	NPV(%)	PLR	NLR
FeNO, ppb	24.50	0.765(0.710-0.820)	69.60	72.91	61.27	79.57	1.58	0.26
FVC, % predicted	89.70	0.508(0.443-0.573)	20.00	86.70	48.08	63.77	0.93	0.57
FEV1, % predicted	90.45	0.635(0.574-0.697)	39.20	82.27	57.65	68.72	1.36	0.46
FEV1/FVC, %	77.97	0.739(0.681-0.797)	62.40	80.30	66.10	77.62	1.95	0.29
PEF, % predicted	82.75	0.622(0.560-0.685)	36.80	83.25	57.50	68.15	1.35	0.47
MMEF, % predicted	66.20	0.771(0.719-0.824)	67.20	78.33	65.63	79.50	1.91	0.26
MEF75, % predicted	81.85	0.717(0.660-0.773)	49.60	83.25	64.58	72.84	1.82	0.37
MEF50, % predicted	73.70	0.780(0.729-0.830)	67.20	76.85	64.12	79.19	1.79	0.26
MEF25, % predicted	54.85	0.731(0.675-0.788)	62.40	78.33	63.93	77.18	1.77	0.30

Data are expressed as mean (SD) or median (range), unless indicated otherwise.

AUC, Area under the curve; FeNO, fractional exhaled nitric oxide; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; PEF, peak expiratory flow; MMEF, forced expiratory flow between 25 and 75%; MEF75, forced expiratory flow at 75% of the FVC; MEF50, forced expiratory flow at 50% of the FVC; MEF25, forced expiratory flow at 25% of the FVC; PPV, positive predictive values; NPV, negative predictive values; PLR, positive likelihood ratios; NLR, negative likelihood ratios.

*The cutoff points were obtained by maximizing the sum of sensitivity and specificity (maximum Youden index).

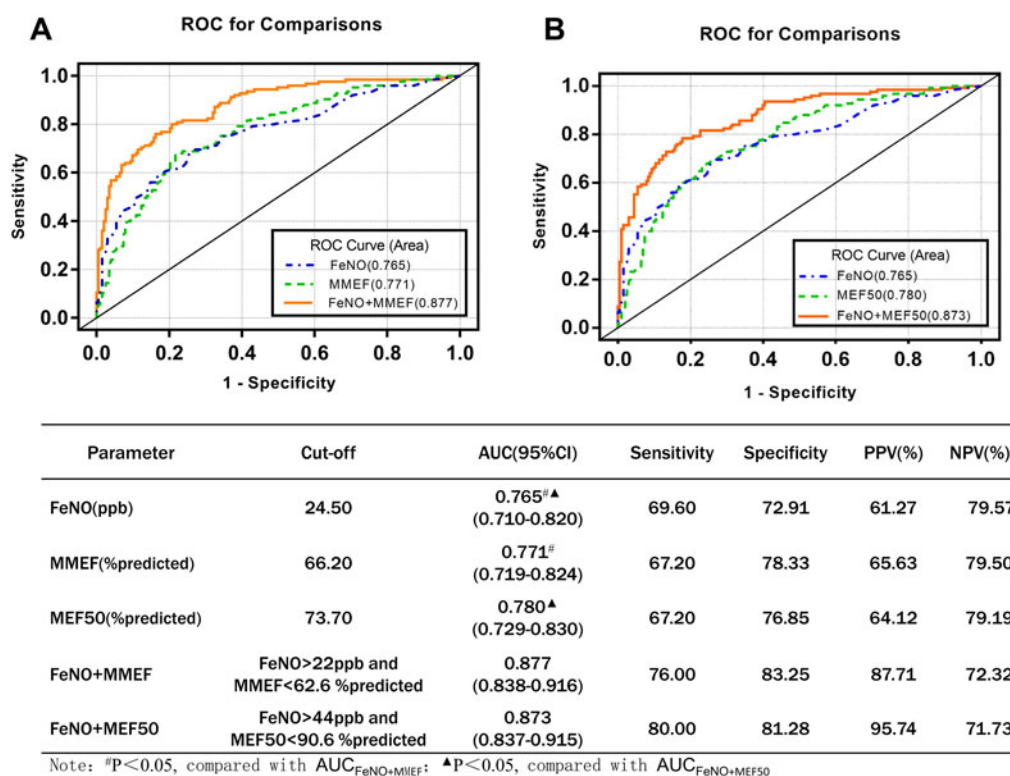


Figure 1. (A) ROC curves for FeNO combined with MMEF in predicting CVA ($n = 328$). (B) FeNO combined with MEF50 in predicting CVA ($n = 328$). AUC, Area under the curve; MMEF, forced expiratory flow at 25–75% of forced vital capacity; MEF50, forced expiratory flow at 50% of the forced vital capacity; FeNO, fractional exhaled nitric oxide.

To increase the diagnostic value, we further performed ROC analysis using indexes combining FeNO and small airway parameters (MMEF or MEF50) (Figure 1). The AUC of FeNO combined with MMEF was 0.877, with optimal cutoff points of 22 ppb for FeNO and 62.6% for MMEF. The AUC for the combination was significantly higher than the AUCs of FeNO or MMEF alone ($P < 0.05$). Additionally, the AUC of FeNO combined with MEF50 was 0.873, with optimal cutoff points of 44 ppb for FeNO and 90.6% for MEF50. The AUC of the combination was also significantly higher than the AUCs of either parameter alone ($P < 0.05$).

FeNO levels increase when patients have allergic rhinitis. Therefore, ROC curve analysis was performed to determine the ability of FeNO alone or in combination with MMEF to distinguish CVA from chronic cough in patients with or without allergic rhinitis (Figure 2). The ROC curve analyses in different groups showed different cutoff levels for FeNO levels: 24.5 ppb (with a sensitivity of 94.44% and a specificity of 55.00%) for rhinitis subjects and 33.5 ppb (with a sensitivity of 40.85% and a specificity of 93.01%) for non-rhinitis subjects. The AUC in rhinitis subjects (0.820) was higher than that in non-rhinitis subjects

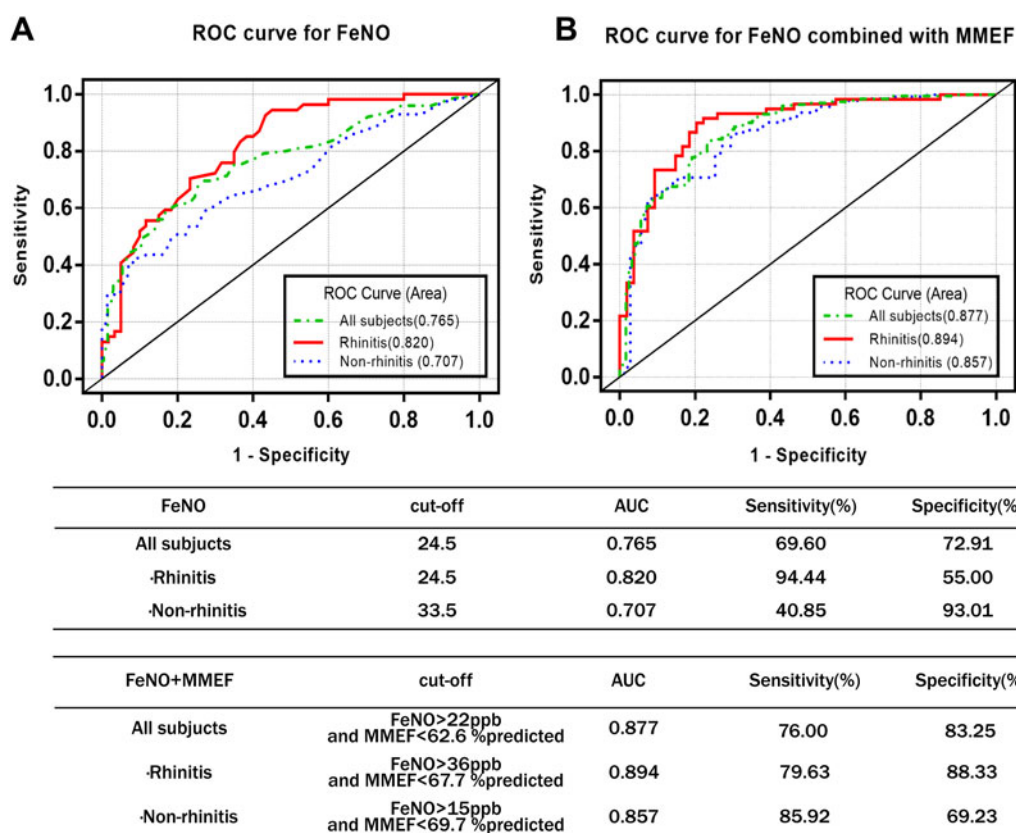


Figure 2. (A) ROC curve analysis of FeNO for CVA diagnosis. (B) ROC curve analysis of FeNO combined with MMEF for CVA diagnosis. AUC, Area under the curve; FeNO, fractional exhaled nitric oxide; MMEF, forced expiratory flow at 25–75% of forced vital capacity.

(0.707) (Figure 2A). For rhinitis subjects, the AUC of FeNO combined with MMEF was 0.894, with a sensitivity of 79.63% and a specificity of 88.33%. The cut-off point for identifying CVA from chronic cough was 36 ppb for FeNO and 67.7% for MMEF. For non-rhinitis subjects, the AUC of FeNO combined with MMEF was 0.857, with a sensitivity of 85.92% and a specificity of 69.23%. The cutoff point for identifying CVA from chronic cough was 15 ppb for FeNO and 69.7% for MMEF.

Discussion

Cough is an important defense mechanism of the human body that can help discharge respiratory secretions. However, long-term cough may cause hoarseness, anxiety, insomnia and other discomforts, greatly affecting the daily lives of patients. Chronic cough (>8 weeks) is one of the most widespread and troublesome nonspecific symptoms in patients visiting respiratory clinics (19). Asthma is one of the main causes of chronic cough. The results of our study indicated that CVA accounted for approximately 40% of patients with chronic cough. Lai et al (20) showed

that CVA accounted for 32.6% of chronic cough. The possible reasons for this inconsistency might be differences in the selection criteria and retrospective bias. The diagnosis of CVA is based on laboratory evidence of BHR and therapeutic efficacy (1). However, the BHR test is expensive, time-consuming and has highly technical requirements for operators, which limits its popularization. In contrast, with the advantages of safety, rapidity and simplicity, spirometry and FeNO tests are available in most primary hospitals. In this study, we investigated the value of MMEF and FeNO in differentiating CVA patients among those chronic cough. Because FeNO is affected by allergic diseases such as allergic rhinitis, additional analysis was performed to evaluate the effects of allergic rhinitis.

The results of our study showed that FeNO, MMEF and MEF50 might be effective indicators for distinguishing between CVA and NCVA. The sensitivity, specificity, positive predictive value and negative predictive value of FeNO for predicting CVA were 69.60%, 72.91%, 61.27% and 79.57%, respectively. The cutoff point was 24.5 ppb. Kowal et al (9) found that the optimal diagnostic cutoff point for FeNO was 40 ppb (sensitivity, 88.3%, specificity,

82.6%). Yi F et al (21) showed that FeNO could be used to distinguish CVA from chronic cough, and the best cutoff point was 33.5 ppb (sensitivity, 69.6%, specificity, 85.1%). Our study showed lower optimal cutoff points and specificity, a possible explanation for which might be the differences in inclusion criteria and sample size. In addition, our study showed that the negative predictive value of CVA for FeNO, MMEF and MEF50 is higher than the positive predictive value. This means that low FeNO, high MMEF and high MEF50 are more likely to exclude asthma, while patients with high FeNO, low MMEF and low MEF50 need further examinations to determine the cause.

Allergic rhinitis is a common chronic airway disease that is similar to asthma in terms of pathogenesis, mechanism, heritability, local pathology, and immunity (22). Consistent with previous studies, in our study, the proportion of patients with allergic rhinitis in the CVA group was much higher than that in NCVA group. Prior reports have shown that FeNO has a certain value for the diagnosis of allergic rhinitis (23), and several studies have shown that asthma patients with allergic rhinitis have higher FeNO values than do those without allergic rhinitis (15, 24). Besides, it is now well established that airway inflammation due to asthma occurs mainly in the small airways, which play a major role in the pathophysiology of asthma (25). Small airway dysfunction exists in patients with both severe and mild asthma. Malerba et al (14) found that MMEF might be a marker for predicting asthma by analyzing the results of FeNO tests, spirometry, BHR tests and induced sputum examinations in 400 adults with asthma-like symptoms. Muñoz-López et al (26) further confirmed that MMEF was more effective than FEV1 for identifying airway BHR and airway dysfunction. The values of small airway parameters (MMEF, MEF50, and MEF25) in the CVA group were significantly lower than those in the NCVA group. When the MEF50 was <73.70%, the area under the curve was 0.780. When the MMEF was <66.20%, the area under the curve was 0.771. This result suggested that the small airway index had a certain value for the diagnosis of CVA. The AUC of FeNO combined with MMEF was 0.877 (with cutoff points of >22 ppb for FeNO and <62.6% for MMEF), which was significantly higher than the AUCs of FeNO or MMEF alone. The AUC of FeNO combined with MEF50 was 0.873 (with cutoff points of >44 ppb for FeNO and <90.6% for MMEF), which showed significantly better diagnostic value of the combination of parameters for CVA than either parameter alone ($P < 0.05$). The conclusion of

our study is in agreement with the findings of previous studies (27,28). Because the combination of indexes significantly improves the diagnostic value, they may assist in the identification of CVA in chronic cough patients.

Matsunaga et al (29) suggested that the effects of allergic rhinitis and smoking should be considered when interpreting the results of FeNO. Because allergic rhinitis increases FeNO levels, the diagnostic value of FeNO in patients with allergic rhinitis may be overestimated. Therefore, we performed another ROC analysis on the basis of the presence of allergic rhinitis, and found that the diagnostic accuracy of FeNO for predicting CVA in chronic cough patients with allergic rhinitis was higher than in chronic cough patients without allergic rhinitis. The optimal cutoff value of FeNO for differentiating CVA from chronic cough patients with allergic rhinitis was >24.5 ppb (sensitivity: 94.44%, specificity: 55.00%). The optimal cutoff value of FeNO for differentiating CVA from chronic cough in patients without allergic rhinitis was >33.5 ppb (sensitivity: 40.85%, specificity: 93.01%), suggesting that the reduction in FeNO suggests NCVA in chronic cough patients, especially in patients without allergic rhinitis.

There were limitations in our study. First, because this was a retrospective study, some of the inherent defects and potential bias were unavoidable. Second, FeNO as a biomarker might be influenced by factors such as smoking. We tried to exclude cases that may affect the results. Finally, we did not obtain complete data regarding blood and induced sputum tests, resulting in the inability to analyze the association between eosinophils and FeNO.

In conclusion, FeNO and MMEF might be useful for identifying CVA in patients with chronic cough and might have a greater value as a negative predictive parameter in distinguishing CVA. The combination of FeNO and MMEF (or MEF50) provided a significantly better prediction of CVA than did either parameter alone. When FeNO is >22 ppb and MMEF <62.6%, the predictive value for the diagnosis of CVA is the highest. Besides, it is worth noting that FeNO >24.5 ppb is sensitive for the prediction of CVA in chronic cough patients with allergic rhinitis, while FeNO >33.5 ppb is specific in patients without allergic rhinitis.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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References

1. Irwin RS, Baumann MH, Bolser DC, Boulet L-P, Braman SS, Brightling CE, Brown KK, Canning BJ, Chang AB, Dicipinigitis PV, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. *Chest*. 2006; 129(1):1S–23S.
2. Corrao WM, Braman SS, Irwin RS. Chronic cough as the sole presenting manifestation of bronchial asthma. *N Engl J Med*. 1979;300(12):633–637. doi:10.1056/NEJM197903223001201.
3. Lai K. Chinese National Guidelines on Diagnosis and Management of Cough: consensus and controversy. *J Thorac Dis*. 2014;6(Suppl 7):S683–S688.
4. Lai K, Li B, Wang F, et al. Survey on the diagnosis and management of the patients with chronic cough. *Int J Respir*. 2011;31:645–647.
5. Mummadi SR, Hahn PY. Update on exhaled nitric oxide in clinical practice. *Chest*. 2016;149(5):1340–1344.
6. Chatkin J M, Ansarin K, Silkoff P E, McCLEAN P, Gutierrez C, Zamel NOE, Chapman K R. Exhaled nitric oxide as a noninvasive assessment of chronic cough. *Am J Respir Crit Care Med*. 1999;159(6):1810–1813.
7. Smith AD, Cowan JO, Filsell S, McLachlan C, Monti-Sheehan G, Jackson P, Taylor DR. Diagnosing asthma: comparisons between exhaled nitric oxide measurements and conventional tests. *Am J Respir Crit Care Med*. 2004;169(4):473–478.
8. Korevaar DA, Westerhof GA, Wang J, Cohen JF, Spijker R, Sterk PJ, Bel EH, Bossuyt PMM. Diagnostic accuracy of minimally invasive markers for detection of airway eosinophilia in asthma: a systematic review and meta-analysis. *Lancet Respir Med*. 2015;3(4): 290–300.
9. Kowal K, Bodzenta-Lukaszyk A, Zukowski S. Exhaled nitric oxide in evaluation of young adults with chronic cough. *J Asthma*. 2009;46(7):692–698. doi:10.1080/02770900903056187.
10. Oh M-J, Lee J-Y, Lee B-J, Choi D-C. Exhaled nitric oxide measurement is useful for the exclusion of non-asthmatic eosinophilic bronchitis in patients with chronic cough. *CHEST*. 2008;134(5):990–995.
11. Song W-J, Kim HJ, Shim J-S, Won H-K, Kang S-Y, Sohn K-H, Kim B-K, Jo E-J, Kim M-H, Kim S-H, et al. Diagnostic accuracy of fractional exhaled nitric oxide measurement in predicting cough-variant asthma and eosinophilic bronchitis in adults with chronic cough: A systematic review and meta-analysis. *J Allergy Clin Immunol*. 2017;140(3):701–709.
12. Hamid Q, Song Y, Kotsimbos TC, Minshall E, Bai TR, Hegele RG, Hogg JC. Inflammation of small airways in asthma. *J Allergy Clin Immunol*. 1997;100(1): 44–51.
13. Perez T, Chanez P, Dusser D, Devillier P. Small airway impairment in moderate to severe asthmatics without significant proximal airway obstruction. *Respir Med*. 2013;107(11):1667–1674.
14. Malerba M, Radaeli A, Olivini A, Damiani G, Ragnoli B, Sorbello V, Ricciardolo FLM. Association of FEF25-75% impairment with bronchial hyperresponsiveness and airway inflammation in subjects with asthma-like symptoms. *Respiration*. 2016;91(3):206–214.
15. Battaglia S, den Hertog H, Timmers MC, et al. Small airways function and molecular markers in exhaled air in mild asthma. *Thorax*. 2005;60(8):639–644.
16. Cheng L, Chen J, Fu Q, He S, Li H, Liu Z, Tan G, Tao Z, Wang D, Wen W, et al. Chinese society of allergy guidelines for diagnosis and treatment of allergic rhinitis. *Allergy Asthma Immunol Res*. 2018;10(4): 300–353. doi:10.4168/aaair.2018.10.4.300.
17. American Thoracic Society; European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide. *Am J Respir Crit Care Med*. 2005;171: 912–930.
18. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005; 26(2):319–338. doi:10.1183/09031936.05.00034805.
19. Smith JA, Woodcock A. Chronic cough. *N Engl J Med*. 2016;375(16):1544–1551. doi:10.1056/NEJMcp1414215.
20. Lai K, Chen R, Lin J, Huang K, Shen H, Kong L, Zhou X, Luo Z, Yang L, Wen F, et al. A prospective, multicenter survey on causes of chronic cough in China. *Chest*. 2013;143(3):613–620. doi:10.1378/chest.12-0441.
21. Yi F, Chen R, Luo W, Xu D, Han L, Liu B, Jiang S, Chen Q, Lai K. Validity of fractional exhaled nitric oxide in diagnosis of corticosteroid-responsive cough. *Chest*. 2016;149(4):1042–1051. doi:10.1016/j.chest.2016.01.006.
22. Shimoda T, Obase Y, Kishikawa R, Iwanaga T, Miyatake A, Kasayama S. The fractional exhaled nitric oxide and serum high sensitivity C-reactive protein levels in cough variant asthma and typical bronchial asthma. *Allergol Int*. 2013;62(2):251–257. doi:10.2332/allergolint.12-OA-0515.
23. Takeno S, Okabayashi Y, Kohno T, Yumii K, Hirakawa K. The role of nasal fractional exhaled nitric oxide as an objective parameter independent of nasal airflow resistance in the diagnosis of allergic rhinitis. *Auris Nasus Larynx*. 2017;44(4):435–441. doi:10.1016/j.anl.2016.09.007.
24. Zhu Z, Xie Y, Guan W, Gao Y, Xia S, Zhong N, Zheng J. FeNO for detecting lower airway involvement in patients with allergic rhinitis. *Exp Ther Med*. 2016;12(4):2336–2340. doi:10.3892/etm.2016.3616.
25. Tulic MK, Christodoulouopoulos P, Hamid Q. Small airway inflammation in asthma. *Respir Res*. 2001;2(6): 333–339. doi:10.1186/rr83.
26. Munoz-Lopez F, Rios-Alcolea M. The interest of FEF(25-75) in evaluating bronchial hyperresponsiveness with the methacholine test. *Allergol Immunopathol (Madr)*. 2012;40:352–356.
27. Bao W, Zhang X, Lv C, Bao L, Yin J, Huang Z, Wang B, Zhou X, Zhang M. The Value of Fractional Exhaled Nitric Oxide and Forced Mid-Expiratory Flow as

- Predictive Markers of Bronchial Hyperresponsiveness in Adults with Chronic Cough. *J Allergy Clin Immunol Pract.* 2018;6(4):1313–1320. doi:[10.1016/j.jaip.2017.09.026](https://doi.org/10.1016/j.jaip.2017.09.026).
28. Feng-Jia C, Xin-Yan H, Geng-Peng L, Yang-Li L, Can-Mao X. Validity of fractional exhaled nitric oxide and small airway function indices in diagnosis of cough-variant asthma. *J Asthma.* 2018;55(7):750–755. doi:[10.1080/02770903.2017.1366509](https://doi.org/10.1080/02770903.2017.1366509).
29. Matsunaga K, Hirano T, Akamatsu K, Koarai A, Sugiura H, Minakata Y, Ichinose M. Exhaled nitric oxide cutoff values for asthma diagnosis according to rhinitis and smoking status in Japanese subjects. *Allergol Int.* 2011; 60(3):331–337. doi:[10.2332/allergolint.10-OA-0277](https://doi.org/10.2332/allergolint.10-OA-0277).