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Diagnostic value of fractional exhaled nitric oxide in cough-variant asthma: an updated meta-analysis

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ABSTRACT
Objective: We aimed to evaluate the diagnostic value of fractional exhaled nitric oxide (FeNO) in cough-variant asthma (CVA) detection. Methods: Relevant studies on the FeNO test in patients with CVA were retrieved from electronic databases including PubMed, Medline, Springer, Elsevier Science Direct, the Cochrane Library, and Google Scholar, up to August 2018. Meta-analysis for sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) of the FeNO test were conducted after extracting related data from the included studies. Meta-DiSc 1.4 and Stata 12.0 software were applied to perform the meta-analysis. Results: In total, 12 studies involving 1968 participants were selected for the meta-analysis. The pooled results of the FeNO test for CVA diagnosis showed that the sensitivity was 0.74 (95% confidence interval [CI] = 0.70 to 0.77), specificity was 0.82 (95% CI = 0.80 to 0.84), PLR was 4.15 (95% CI = 3.04 to 5.65), NLR was 0.30 (95% CI = 0.22 to 0.41), and DOR was 15.33 (95% CI = 8.43 to 27.86). The area under the curve and Q² index were 0.87 and 0.80, respectively. Moreover, no significant publication bias was observed using Egger’s linear regression test (P > 0.05). Conclusion: The FeNO test might be an appropriate diagnostic tool for CVA detection.

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KEYWORDS
Fractional exhaled nitric oxide; cough-variant asthma; likelihood ratio; diagnostic odds ratio; area under the curve; meta-analysis

Introduction
Cough-variant asthma (CVA) is a subtype of asthma characterized primarily by chronic cough, rather than wheezing, which occurs in approximately 30% of individuals with CVA, although it can progress to a more typical asthma presentation [1–3]. Similar to typical asthma, bronchial hyperresponsiveness, IgE-dependent type I allergic reaction, Type 2 inflammation and calculation of eosinophilic infiltration play important roles in the pathogenesis of CVA [4–6]. Fractional exhaled nitric oxide (FeNO) level change correlates with eosinophilic airway inflammation [7], but it is more accurately representative of Type 2 inflammation driven by IL-13 [8–10]. Alving et al. [11] have found the increased level of FeNO in patients with asthma in 1993. Subsequently, FeNO has been evaluated as a diagnostic tool in asthma, including CVA [12], as it is a simple, sensitive, and noninvasive measure that can help monitor airway inflammation [13].

Many studies have reported that FeNO levels are elevated in patients with bronchial asthma and CVA; however, the diagnostic value of the FeNO test for detecting CVA remains discordant [14–16]. For example, Yi et al. have shown that the sensitivity of FeNO is insufficient to rule out the diagnosis of CVA [14], while Feng et al. demonstrated that FeNO test is a rapid and valuable diagnostic method for patients with CVA [17], and Pizzimenti et al. showed that the FeNO test is useful in CVA diagnosis [11]. Given the limited sample sizes and discordant conclusions of previous individual studies, the role of FeNO test in CVA diagnosis needs to be further clarified. In 2017, a meta-analysis was performed to evaluate the diagnostic accuracy of FeNO in detecting CVA and eosinophilic bronchitis in patients with chronic cough [18], but most of their included studies regarding CVA were published in China and only two studies were published within recent 3 years. Therefore, in the present study, a systematic review and updated meta-analysis were conducted to quantitatively combine the results of more eligible studies published within recent 3 years in different countries to evaluate the diagnostic role of FeNO in CVA separately.

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Methods

Search strategy

Relevant studies on the FeNO test in patients with CVA published in English were retrieved from electronic databases including PubMed, Medline, Springer, Elsevier Science Direct, the Cochrane Library, and Google Scholar up to August 2018. The studies were retrieved using the following key words: (“fractional exhaled nitric oxide” or “FeNO”) and (“cough-variant asthma” or “CVA” or “cough variant asthma”) and (“diagnosis” or “diagnostic”) and (“study” or “trial” or “research”). In addition, in order to obtain more relevant studies, references from the included articles were also retrieved.

Study selection

The electronic databases were independently searched by four investigators. Studies from the independent electronic databases were retrieved by two researchers by using the same method. Disagreements were resolved by discussion or consultation with a third reviewer.

Inclusion and exclusion criteria

The studies were included if the protocol met the following criteria: subjects with constant cough more than 3 weeks; normal plain chest radiographic or computed tomographic findings; no pulmonary disease treatment history including oral or inhaled corticosteroids; no history of smoking or being a former smoker of more than five pack-years; as well as no respiratory tract infection or allergic rhinitis attacks within 4 weeks of the study. The FeNO levels were further evaluated as an assisted diagnosis for CVA. The data on sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) were provided or could be calculated in the individual studies. Reviews, reports, and duplicated studies were excluded from the meta-analysis.

Quality evaluation and data extraction

Quality evaluation was performed on the basis of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) criteria [19,20]. Information including study details (e.g., name of the first author, year of publication, participant’s location, and study design) and characteristics of the participants (e.g., age and sample size) were extracted using the predesigned protocol. Furthermore, the data and extracted information were confirmed by a third investigator. To obtain further information, the authors of the included studies were contacted to verify data that needed clarification. When discrepancies occurred, researchers in the research team participated in the course of information confirmation, or the original investigators were contacted to confirm the data.

Meta-analysis

The performance of diagnostic test was evaluated using the summary receiver operating characteristic (SROC) curve [21]. The maximal value points of the SROC curve were designated as cutoff points, and multiple points in the curve were the value summations of sensitivity and specificity [22]. The area under the curve (AUC) was an important index for sensitivity and specificity evaluation, and heterogeneity among individual studies was evaluated using the Q statistic [21]. In addition, index Q*, calculated at the point on the SROC curve where sensitivity and specificity are equal, is used to assess diagnostic value [21]. The cutoff value of index Q* is similar with AUC, where a Q* between 0.7–0.9 represents a good diagnostic value and larger than 0.9 represents an excellent diagnostic value. The asymmetry of the funnel was measured using the natural logarithmic scale of the effect size. Moreover, Egger’s linear regression [23] was used to evaluate publication bias.

The meta-analysis was performed using Meta-DiSc v.1.4 software (Hospital Universitario Ramón y Cajal, Madrid, Spain) and STATA package v.12.0 (Stata Corporation, College Station, TX, USA). Two-sided p values were evaluated, and \( P < 0.05 \) was defined as statistically significant.

Results

Characteristics of eligible studies

In total, 774 papers involving the diagnostic value of FeNO in CVA were originally obtained (including 231 articles from PubMed, 131 from Medline, 81 from Springer, 69 from Elsevier Science Direct, 11 from the Cochrane Library, and 251 from Google Scholar). A detailed flow diagram illustrating study selection is shown in Figure 1. After removing duplicates and irrelevant articles, 51 potentially relevant studies were selected. After reading the abstracts of these studies,
27 were excluded, including 15 reviews, 7 articles without information on the FeNO test, and 5 articles without CVA information. Thereafter, we fully reviewed the remaining 24 articles and then excluded 12 of them, including 5 without comparison and 7 without data that could be extracted or calculated. Finally, 12 studies were enrolled in the meta-analysis [12,14–17,24–30].

Table 1 lists the baseline characteristics of the 12 enrolled studies that include a total of 1968 participants. The publication year of the enrolled articles ranged from 2008 to 2017, and the included sample size in included studies ranged from 52 to 450. The criteria for the diagnosis of CVA followed the current international or national clinical guidelines [31–38], which was a combination of the following criteria: (1) constant cough with wheezing >3 weeks; (2) positive airway hyperresponsiveness or presence of reversible airflow limitation or daytime variability rate of peak expiratory flow >20%; (3) normal spirometry from pulmonary function test; and (4) response to anti-asthmatic therapy. In addition, the expiratory flow rate for FeNO test set in all studies was 50 mL/s, except for the Pizzimenti et al.’s study, in which the data for this parameter was not provided.

Detailed information on quality assessment is presented in Table 2. Information on patient representation, reference standard, and uninterruptable/intermediate test reporting were absent in some of the included studies. The majority of items were reported in each included study. Overall, the quality of each individual study was relatively high.
Overall effects of the diagnostic parameters of the FeNO test for CVA

Spearman correlation coefficient for the study was 0.483, and the \( p \) values were 0.64, suggesting no significant threshold effect in this study. The overall effects of the diagnostic parameters of the FeNO test for CVA were further analyzed. The meta-analysis results of the FeNO test for CVA diagnosis are summarized in Table 3. The random-effect model was used to combine the data because of significant heterogeneity among the included studies (\( Q^2 = 4.44, I^2 = 55.0\% \), \( P < 0.1 \)). The overall estimate showed that the FeNO test might be appropriate for detecting patients with CVA. For the diagnostic accuracy of the FeNO test for CVA, the pooled value of sensitivity was 0.74 (95% confidence interval (CI) = 0.70 to 0.77), specificity was 0.82 (95% CI = 0.80 to 0.84), PLR was 4.15 (95% CI = 3.04 to 5.65), NLR was 0.30 (95% CI = 0.22 to 0.41), and DOR was 15.33 (95% CI = 8.43 to 27.86) (Figure 2). The pooled AUC and \( Q/C \) index were 0.8741 and 0.8045, respectively.

Publication bias was assessed using data shown in Table 3. No significant publication bias (\( t = 1.88, P > 0.05 \)) was shown in the studies.

In order to evaluate the diagnostic value of FeNO for CVA, relevant studies evaluating the efficacy of FeNO for CVA diagnosis were retrieved. In the present meta-analysis, data from 12 separate studies involving 1668 patients were combined, and the pooled data (sensitivity: 0.74; specificity: 0.82; PLR: 4.15; NLR: 0.30; AUC: 0.8741; and \( Q/C \) index: 0.8045) in our study suggested that the FeNO test appeared to be a valuable, although not perfect tool for CVA diagnosis.

The activity of inducible nitric oxide synthase (iNOS) in epithelial cells is increased in the presence of persistent chronic airway inflammation in asthma, thereby resulting in a significant increase in NO levels detected in exhaled breath [39]. Recent evidence further demonstrates that the upregulation of iNOS in respiratory epithelium is induced by airway inflammation via activation of STAT-6 and Th2-cytokines interleukin (IL)-4 and IL-13 in patients with asthma, and this inflammation is corticosteroid-resistant [40].

Table 2. Quality assessment of the included articles.

<table>
<thead>
<tr>
<th>QUADAS list item</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Did the spectrum of patients represent the patients who will receive the test in practice?</td>
<td>++</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>2. Were selection criteria clearly described?</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>3. Is the reference standard likely to correctly classify the target condition?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>4. Is the period between the reference standard and index test short enough to be reasonably sure that the target condition did not change between the 2 tests?</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>5. Did the entire sample or a random selection of the sample receive verification using a reference standard of diagnosis?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>6. Did patients receive the same reference standard regardless of index test result?</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>7. Was the reference standard independent of the index test (i.e., index test did not form part of the reference standard)?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>8. Was execution of the index test described in sufficient detail to permit replication of the test?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>9. Was execution of the reference standard described in sufficient detail to permit its replication?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
<td></td>
</tr>
<tr>
<td>10. Were index test results interpreted without knowledge of results of the reference standard?</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>11. Were reference standard results interpreted without knowledge of results of the index test?</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>13. Were uninterruptable/intermediate test results reported?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>14. Were withdrawals from the study explained?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

Notes: QUADAS: Quality Assessment of Diagnostic Accuracy Studies. ++: YES; +: YES; 0: NO; -: Not clear.
Table 3. The indexes of CVA diagnosis by FeNO test.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test of association</th>
<th>Test of heterogeneity</th>
<th>Egger’s test for publication bias</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimates</td>
<td>95% CI</td>
<td>Q</td>
</tr>
<tr>
<td>Overall</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.74</td>
<td>0.70–0.77</td>
<td>44.39</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.82</td>
<td>0.80–0.84</td>
<td>41.31</td>
</tr>
<tr>
<td>Positive LR</td>
<td>4.15</td>
<td>3.04–5.65</td>
<td>57.41</td>
</tr>
<tr>
<td>Negative LR</td>
<td>0.30</td>
<td>0.22–0.41</td>
<td>52.00</td>
</tr>
<tr>
<td>DOR</td>
<td>15.33</td>
<td>8.43–27.86</td>
<td>61.62</td>
</tr>
</tbody>
</table>

DOR: Diagnostic odds ratio; LR: likelihood ratio.

Figure 2. Diagnostic value of the fractional exhaled nitric oxide (FeNO) test in cough-variant asthma diagnosis. A: Sensitivity of the FeNO test; B: Specificity of the FeNO test; C: Positive likelihood ratio of the FeNO test; D: Negative likelihood ratio of the FeNO test; E: Diagnostic odds ratio of the FeNO test.

Figure 3. Summary receiver operating characteristic curve of the FeNO test for cough-variant asthma diagnosis.
responsive [40]. Choi et al. have suggested that FeNO levels are associated with eosinophil counts and bronchial mucosal eosinophil activity in bronchial-induced sputum and bronchoalveolar lavage fluid [41]. It has also been suggested that FeNO level is a representative marker of Type-2 inflammation, but not general eosinophilic inflammation, and FeNO measurement is beneficial for identification of asthma patients with Type-2 inflammation and inhaled corticosteroids responsiveness [42]. The absence of a correlation between FeNO and eosinophilic inflammation is reported in the study of Corren et al., which shows that treatment with lebrikizumab, an anti-IL-13 mAb, significantly reduces FeNO levels in adults with asthma, but does not reduce blood eosinophil count [43]. In addition, it has been reported that FeNO level is not a significant single predictor of composite airway eosinophil status in asthmatic patients [44].

In this study, we used DOR, AUC, and other indicators to evaluate the diagnostic value of FeNO for CVA. The DOR value reflected the correlation between diagnostic value of FeNO and CVA. Generally, DOR value > 1 indicates that the diagnostic value of test was good. Notably, in the present study, the DOR value of FeNO for CVA diagnosis was 15.33, indicating that FeNO could be considered a diagnostic marker for CVA. Simultaneously, we applied the SROC to show the overall FeNO performance and AUC analysis to assess overall diagnostic efficiency. In general, AUC value and Q* index > 0.9 indicate an excellent diagnostic value, and value and Q* index between 0.7 and 0.9 indicate a good diagnostic value, while AUC and Q* index below 0.5 and 0.7 indicate a poor diagnostic value. Combined with the above criteria, our data indicated that FeNO had a good diagnostic value (AUC = 0.8741 and Q* index = 0.8045). Meanwhile, significantly increased level of FeNO in patients with CVA has been verified by many researchers [15,45]. Therefore, data from this study demonstrated that FeNO might be a potentially valuable tool for diagnosing CVA.

The present study had several limitations. Significant heterogeneity was detected during pooling the data from included studies, which might be due to the different FeNO detection methods and study locations. In addition, the thresholds of FeNO used to diagnose CVA in the included studies were varied, which might indicate the use of different gold standards and study designs in diagnosing CVA. The degree of heterogeneity is an important factor affecting the validity of the results of a meta-analysis [46]. Although significant heterogeneity of the studies was detected, the included studies had a rather consistent result. Additionally, a subgroup analysis wasn’t performed because of the limited enrolled sample size and limited number of included studies. Thus, further studies with larger sample sizes and homogeneous data should be designed to verify the current conclusions.

**Conclusions**

The FeNO test may be a useful diagnostic tool for CVA, with a high diagnostic value. However, further studies with larger sample sizes and subgroup analysis are needed to confirm the current conclusions.

**Funding**

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