

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

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Background: Individual studies have suggested the utility of fractional exhaled nitric oxide (FENO) measurement in detecting cough-variant asthma (CVA) and eosinophilic bronchitis (EB) in patients with chronic cough.

Objective: We sought to obtain summary estimates of diagnostic test accuracy of FENO measurement in predicting CVA, EB, or both in adults with chronic cough.

Methods: Electronic databases were searched for studies published until January 2016, without language restriction.

Cross-sectional studies that reported the diagnostic accuracy of FENO measurement for detecting CVA or EB were included.

Risk of bias was assessed with Quality Assessment of Diagnostic Accuracy Studies 2. Random effects meta-analyses were performed to obtain summary estimates of the diagnostic accuracy of FENO measurement.

Results: A total of 15 studies involving 2187 adults with chronic cough were identified. FENO measurement had a moderate diagnostic accuracy in predicting CVA in patients with chronic

cough, showing the summary area under the curve to be 0.87 (95% CI, 0.83-0.89). Specificity was higher and more consistent than sensitivity (0.85 [95% CI, 0.81-0.88] and 0.72 [95% CI, 0.61-0.81], respectively). However, in the nonasthmatic population with chronic cough, the diagnostic accuracy to predict EB was found to be relatively lower (summary area under the curve, 0.81 [95% CI, 0.77-0.84]), and specificity was inconsistent.

Conclusions: The present meta-analyses indicated the diagnostic potential of FENO measurement as a rule-in test for detecting CVA in adult patients with chronic cough. However, FENO measurement may not be useful to predict EB in nonasthmatic subjects with chronic cough. These findings warrant further studies to validate the roles of FENO measurement in clinical practice of patients with chronic cough. (*J Allergy Clin Immunol* 2017;■■■:■■■-■■■.)

Key words: Chronic cough, fractional exhaled nitric oxide, asthma, eosinophilic bronchitis, systematic review

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Supported by grant no. 23-2015-0200 from the SNUH Research Fund.

Disclosure of potential conflict of interest: W.-J. Song receives grant support from Seoul National University Hospital. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication June 3, 2016; revised October 28, 2016; accepted for publication November 2, 2016.

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0091-6749/\$36.00

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<http://dx.doi.org/10.1016/j.jaci.2016.11.037>

Chronic cough is a common medical condition with a significant effect on quality of life.^{1,2} Several intrinsic and extrinsic factors can contribute to hypersensitivity in the cough reflex, and T_H2 cell-mediated airway inflammation is one of the major triggers of this condition.^{3,4} The diagnostic approaches for cough-variant asthma (CVA) and eosinophilic bronchitis (EB), 2 common conditions with T_H2 inflammation, have been an integral part of the clinical guidelines for chronic cough.^{5,6} Notably, these are particular conditions in which objective diagnostic tests are preferred to empiric treatment in suspected patients during the early stages of their diagnostic work-up.^{5,6} However, the tests required for diagnosing CVA and EB, such as bronchial challenge tests and induced sputum analyses, are technically demanding and require specialized instruments and personnel.⁷⁻⁹ Thus their use is restricted to specialist centers.

Since the discovery of the biological roles of endogenous nitric oxide (NO) and the standardization of simple analyzers of exhaled NO in the 1990s,^{10,11} fractional exhaled nitric oxide (FENO) has been suggested as a potential biomarker for T_H2 inflammation.¹² The great advantage of measuring FENO values is that it only requires a simple, rapid, and noninvasive test,¹³ potentially enabling the test to be widely used in clinical practice. International clinical practice guidelines by the American

Abbreviations used

AHR:	Airway hyperresponsiveness
AUC:	Area under the curve
CVA:	Cough-variant asthma
EB:	Eosinophilic bronchitis
FENO:	Fractional exhaled nitric oxide
HSROC:	Hierarchical summary receiver operating characteristic
NO:	Nitric oxide
ROC:	Receiver operating characteristic
RQ:	Research question

Thoracic Society on FENO measurement and interpretation suggest its utility in the diagnosis and monitoring of asthma and also its potential value for chronic obstructive pulmonary disease and pulmonary hypertension.¹³ However, its diagnostic utility can vary with the target population, and no specific recommendation has been made for patients with chronic cough.¹³

Considering convenience and safety, FENO measurement can be integrated into the diagnostic pathway for patients with chronic cough. In the literature individual studies have suggested diagnostic value in detecting CVA or nonasthmatic EB.^{14,15} However, the diagnostic properties of FENO measurement for CVA and EB have not been systematically reviewed within the clinical context of chronic cough. Here we report a systematic review, summarizing the current evidence. We also conducted meta-analyses to obtain summary estimates of diagnostic test accuracy for FENO measurement in predicting CVA, EB, or both in adult patients with chronic cough.

METHODS

Search strategy

We conducted a systematic literature search to identify studies that had relevant information for the following 3 research questions (RQs):

“What is the diagnostic accuracy of FENO (index test) for CVA and/or EB (reference standard) in patients with chronic cough (target condition)?”

- RQ1: FENO for CVA in patients with chronic cough;
- RQ2: FENO measurement for either CVA or EB in patients with chronic cough; and
- RQ3: FENO measurement for EB in nonasthmatic patients with chronic cough.

We searched the PubMed, Embase, Web of Science, and Scopus databases according to the recommendation of the PRISMA statement.¹⁶ The search terms were “cough” AND “nitric oxide” in [all fields] that correspond to the “target condition (chronic cough)” and “index test (FENO),” which are the 2 main components of our RQs. The search encompassed studies published up to January 2016, with no language restriction. We used this search strategy because we previously found that the number of publications was not excessive.¹⁷ Additional searches were performed by using Google Scholar and all cross-referenced articles. Eligibility criteria are provided in the [Methods](#) section in this article’s Online Repository at www.jacionline.org. The study was registered as PROSPERO CRD42016036429 (date of registration: March 15, 2016).

Data extraction

Data were independently extracted by 2 authors. We constructed 2×2 tables describing the index test results for each reported threshold level of FENO values. If 2×2 tables were not described in the original publications, we reconstructed them from summary statistics or calculated them from the information provided by the corresponding authors. Data

extraction methods are detailed in the [Methods](#) section in this article’s Online Repository.

Quality assessment

The methodological quality of the studies included was independently assessed by 2 authors using the Quality Assessment of Diagnostic Accuracy Studies 2 tool, which consists of 4 domains.¹⁸ The details of quality assessment are provided in the [Methods](#) section in this article’s Online Repository.

Statistical analyses

From the constructed 2×2 table, we calculated estimates of sensitivity and specificity, as well as 95% CIs for the individual study. Data were summarized as paired forest plots. Summary ROC curves were created to examine the overall diagnostic properties of FENO measurement in each RQ. We used a random effects hierarchical summary receiver operating characteristic (HSROC) model to adjust for between-study variability in cutoff levels.¹⁹ For the HSROC curve, the individual and summary points for sensitivity and specificity, as well as the 95% confidence region around the summary points and the 95% prediction region, were plotted. The 95% prediction region shows the amount of statistical heterogeneity between studies and predicts the sensitivity and specificity in a future study.

Heterogeneity was assessed first based on visual assessment of forest and HSROC plots. Threshold effects were determined to be likely if the Spearman correlation coefficient between sensitivity and the false positive rate were 0.6 or greater.²⁰ Cook distances were used to identify outliers that influenced the summary estimates. The I^2 statistic was calculated to quantify the unobserved heterogeneity, which describes the percentage of total variation across studies that is attributable to heterogeneity instead of chance.²¹ However, the I^2 statistic is limited in diagnostic test reviews because it does not account for the variation caused by the threshold effect.²² Sensitivity analyses and multivariate meta-regression analyses were performed to further explore the source of heterogeneity. Metaregression was used to evaluate the statistical significance of differences in sensitivity and specificity by study characteristics. In multivariate analyses covariates were selected if they were considered to contribute to the heterogeneity in univariate meta-regression analyses ($P < .05$). Subgroup analyses were performed on multiple predetermined covariates, including cough duration, study design, and outcome definitions. All of the statistical analyses were performed with RevMan software (version 5.3; Cochrane Collaboration, Oxford, United Kingdom) and the meta-analysis modules of Stata (version 14.1; StataCorp, College Station, Tex; metandi and midas).

RESULTS

Study characteristics and methodological quality

In total, 15 studies involving 2187 adult patients with chronic cough were identified to respond to one of the 3 RQs ([Fig 1](#)). Baseline characteristics of the 15 included studies are summarized in [Table E1](#) and the [Results](#) section in this article’s Online Repository at www.jacionline.org. Fourteen studies were published as full articles,^{14,15,23-34} and 1 was a conference abstract.³⁵ Most of the studies were conducted in Asia (10/15; 8 in China, 1 in Korea, and 1 in Japan), and 5 were performed in Europe and Canada. Selection criteria from each included study are summarized in [Table E2](#) in this article’s Online Repository at www.jacionline.org. The studies excluded at the final stage are detailed in [Table E3](#) in this article’s Online Repository at www.jacionline.org.

The most common criterion for defining CVA was the combination of (1) cough (as the sole or predominant symptom); (2) demonstration of airway hyperresponsiveness (AHR), variable airway obstruction, or both; and (3) a good treatment

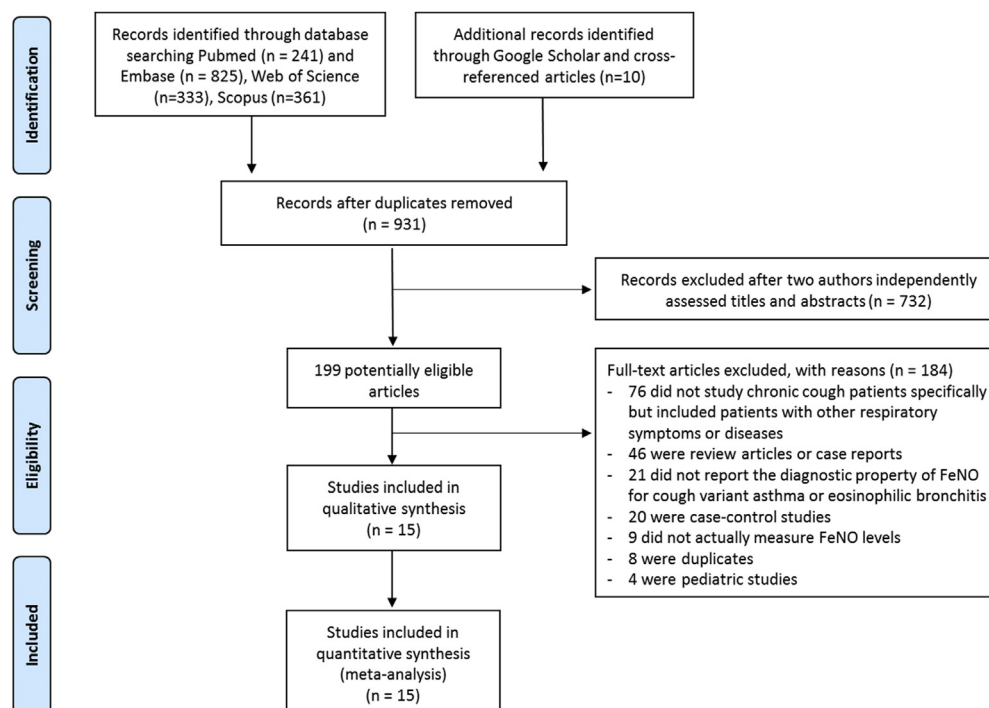


FIG 1. PRISMA for study selection.

response to asthma therapy (10 studies),^{24-27,30-35} which followed current international or national clinical guidelines (thus termed the *guideline-based diagnosis* of CVA).^{5,6,36} The combination of (1) cough and (2) demonstration of AHR, variable airway obstruction, or both was adapted in 5 studies (ie, the *presumed diagnosis* of CVA).^{14,15,23,28,29} The latter was mostly used in the studies published before 2010. EB was defined as induced sputum eosinophilia ($\geq 3\%$ in 2 studies^{15,29}) or the combination of (1) a good treatment response to corticosteroids and (2) induced sputum eosinophilia ($\geq 2.5\%$ in 3 studies,^{24,32,33} $\geq 2\%$ in 1 study,²⁷ and $\geq 3\%$ in 1 study²⁵); here we allowed these variations in the criteria for sputum eosinophilia because each value is used in international or national clinical guidelines.^{5,6,36,37}

The quality of the studies included was assessed by using Quality Assessment of Diagnostic Accuracy Studies 2 (detailed in Fig E1 and the Results section in this article's Online Repository at www.jacionline.org).

RQ1: Diagnostic utility of FeNO measurement for CVA in patients with chronic cough

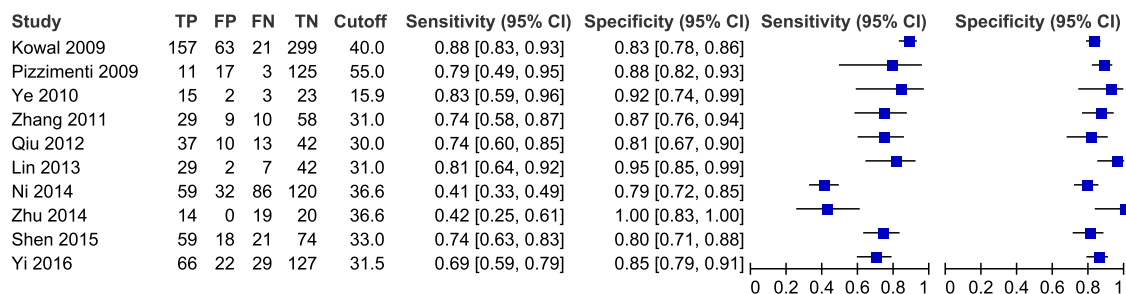
In total, 13 studies (2019 patients) provided diagnostic information on FeNO values for CVA in patients with chronic cough.^{14,15,23,24,26,28-35} Because the definition for chronic cough (≥ 8 vs ≥ 3 weeks) was a potential source of heterogeneity (see Table E4 in this article's Online Repository at www.jacionline.org), we divided the analyses according to the definition. First, we analyzed 10 studies (1793 patients) that defined chronic cough as cough for 8 weeks or longer.^{23,24,26,28,30-35} The findings on diagnostic accuracy are shown as a forest plot (Fig 2, A). Optimal cutoff levels ranged from 15.9 to 55.0 ppb and were between 30 and 40 ppb in 8 of 10 studies. Fig 3, A, shows the HSROC curve for the primary meta-analysis. The visual distribution of 10 optimal diagnostic points obtained from the individual studies

indicated that specificity was higher and more consistent than sensitivity. Sensitivity and specificity were 0.72 (95% CI, 0.61-0.81; 95% prediction, 0.22-0.96; $I^2 = 91.9\%$) and 0.85 (95% CI, 0.81-0.88; 95% prediction, 0.74-0.91; $I^2 = 47.6\%$), respectively. Spearman correlation tests for sensitivity and false positive rate suggested that the heterogeneity was likely to be due to nonthreshold effects ($r = -0.309$, $P = .385$). The summary area under the curve (AUC) was 0.87 (95% CI, 0.83-0.89; Table I).

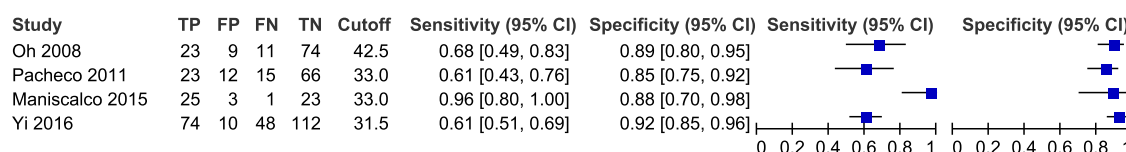
Two studies had notably lower sensitivities,^{26,34} and Cook distance analyses revealed that they^{26,34} were outliers showing a relatively higher proportion of CVA (48.8% and 62.2%, respectively; see Fig E2 in this article's Online Repository at www.jacionline.org). In linear regression analyses the proportion of CVA was correlated with sensitivity ($r^2 = 0.321$, $P = .087$). These findings led us to speculate whether methodological difference (eg, inclusion criteria) could have influenced the sensitivity. The study by Ni et al²⁶ had a retrospective design and a presumed diagnosis of CVA, whereas the study by Zhu et al³⁴ did not include normal chest x-ray results in their selection criteria (see Tables E1 and E2), suggesting that CVA diagnoses could be confounded in those studies. Thus those studies were excluded from the primary meta-analysis to examine effects. The resultant sensitivity and specificity were 0.75 (95% CI, 0.68-0.80) and 0.87 (95% CI, 0.83-0.90), respectively.

Sensitivity analyses were performed to further explore the potential sources of heterogeneity (see Table E5 in this article's Online Repository at www.jacionline.org). Several covariates, including studies from Asian regions, a non-English publication, a retrospective design, use of electrochemical FeNO analyzers, use of a presumed diagnosis of CVA, or the lack of normal chest x-ray results in selection criteria, led to lower sensitivities. In multivariate metaregression analyses the CVA diagnostic criteria and the type of FeNO analyzer were significant sources of

A



B



C

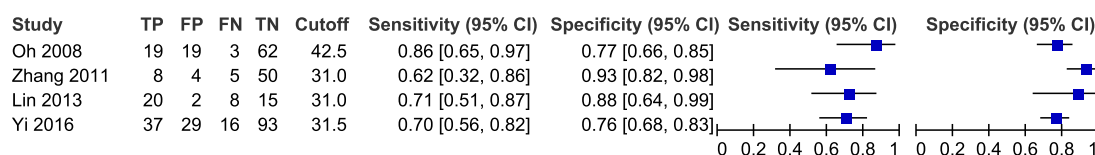


FIG 2. Forest plots on the diagnostic utility of FENO measurement for predicting CVA in 10 studies of patients with chronic cough (defined by cough for ≥ 8 weeks; **A**), predicting either CVA or EB in 4 studies of patients with chronic cough (**B**), and predicting EB in 4 studies of nonasthmatic patients with chronic cough (**C**).

heterogeneity (see [Table E6](#) in this article's Online Repository at www.jacionline.org). Details on meta-regression analyses are provided in the [Results](#) section in this article's Online Repository.

Subgroup analyses were performed on the study design and CVA diagnostic criteria. In the subgroup analysis of prospective studies ($n = 7$, see [Fig E3, A](#), in this article's Online Repository at www.jacionline.org),^{23,28,30,32-35} the sensitivity, specificity, and summary AUC were 0.73 (95% CI, 0.62-0.82; 95% prediction, 0.24-0.96; $I^2 = 84.0\%$), 0.86 (95% CI, 0.82-0.88; 95% prediction, 0.75-0.92; $I^2 = 25.3\%$), and 0.88 (95% CI, 0.84-0.90), respectively ([Fig 3, B](#)). In the subgroup analysis of studies with guideline-based diagnostic criteria for CVA ($n = 7$, see [Fig E3, B](#)),^{24,30-35} the sensitivity, specificity, and summary AUCs were 0.71 (95% CI, 0.61-0.79; 95% prediction, 0.35-0.92; $I^2 = 65.3\%$), 0.88 (95% CI, 0.82-0.92; 95% prediction, 0.66-0.97; $I^2 = 43.1\%$), and 0.89 (95% CI, 0.86-0.91), respectively ([Fig 3, C](#)).

Additional subgroup analyses were performed *post hoc* on studies that met the diagnostic recommendations in current guidelines,^{5,6} and those in which normal chest x-rays and guideline-based diagnostic criteria for CVA were used; 6 studies met these criteria.^{24,30-33,35} Optimal cutoff levels ranged from 15.9 to 55 ppb (median, 36.7 ppb), and 4 studies ranged from 33 to 40 ppb (see [Fig E3, C](#)).^{24,30,32,33} The pooled sensitivity and specificity were 0.75 (95% CI, 0.68-0.80; 95% prediction, 0.60-0.85; $I^2 = 0.0$) and 0.87 (95% CI, 0.83-0.90; 95% prediction, 0.74-0.94; $I^2 = 30.1\%$), respectively, suggesting that a strict

indication of FENO measurement within the diagnostic pathways could result in better sensitivity ([Fig 3, D](#)).

There were 3 studies (226 patients) with cough of 3 weeks or longer (see [Fig E4](#) in this article's Online Repository at www.jacionline.org).^{14,15,29} This pool was enriched with unpublished data from one study¹⁵ that were obtained by contacting the corresponding author. However, the minimum required number ($n = 4$) for performing a meta-analysis was not met. The optimal cutoff level ranged from 30.0 to 42.5 ppb. Sensitivity and specificity were in the range of 0.62 to 0.79 and 0.77 to 0.91, respectively.

RQ2: Diagnostic utility of FENO measurement for either CVA or EB in patients with chronic cough

Four studies of 529 patients were analyzed ([Fig 2, B](#)).^{15,25,27,32} This analysis was enriched with unpublished data from the study by Oh et al.¹⁵ Optimal cutoff levels ranged from 31.5 to 42.5 ppb. Sensitivity was 0.72 (95% CI, 0.61-0.81; 95% prediction, 0.01-0.99; $I^2 = 77.7\%$); one study²⁵ showed a particularly high sensitivity value of 0.96, whereas others showed lower values (range, 0.61-0.68). Specificity was 0.85 (95% CI, 0.81-0.88; 95% prediction, 0.69-0.97; $I^2 = 7.5\%$). The HSROC curve analyses estimated the summary AUC to be 0.89 (95% CI, 0.86-0.92; [Fig 4](#)). Heterogeneity, particularly with regard to sensitivity, was suggested by the HSROC curve appearance;

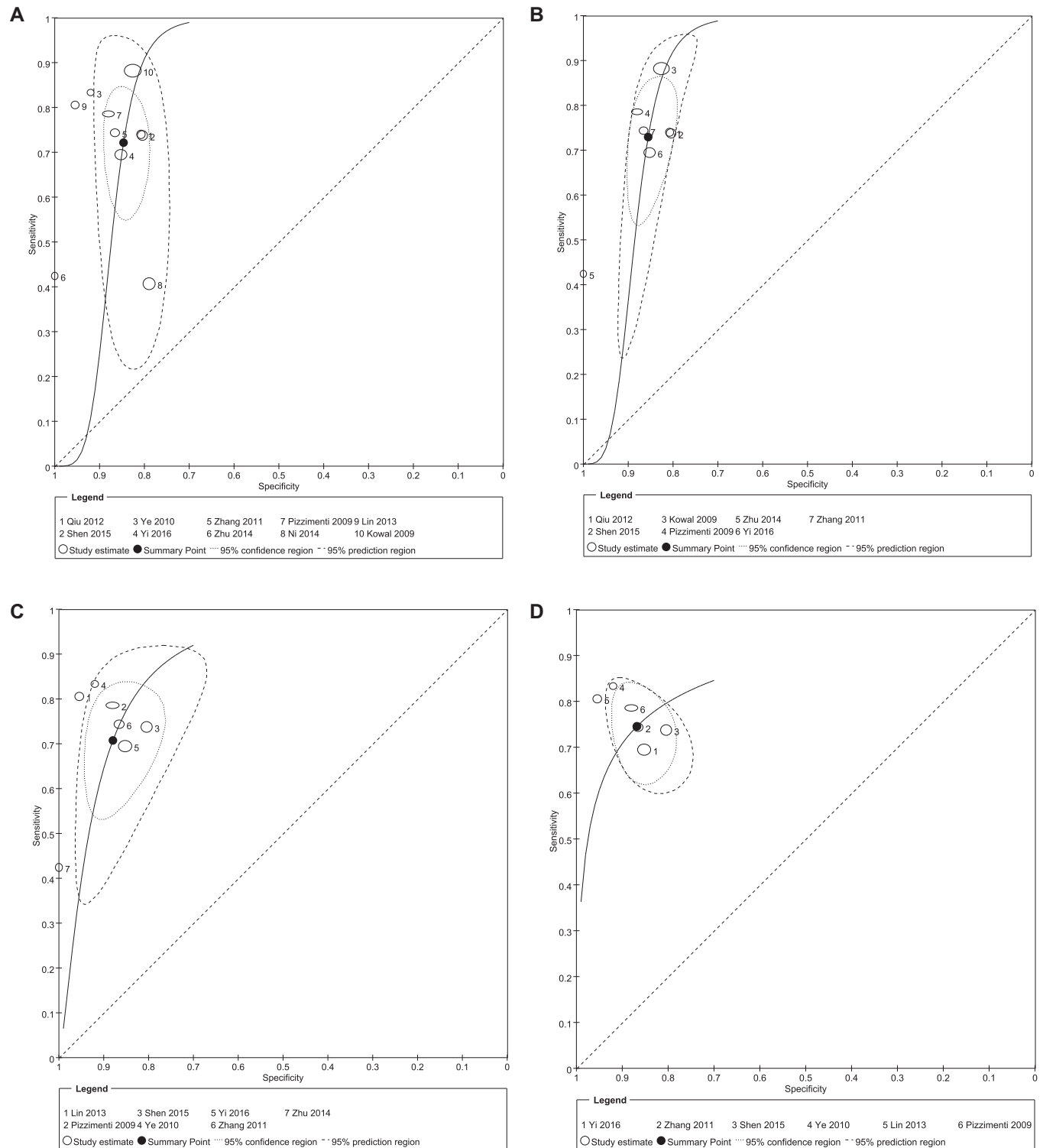
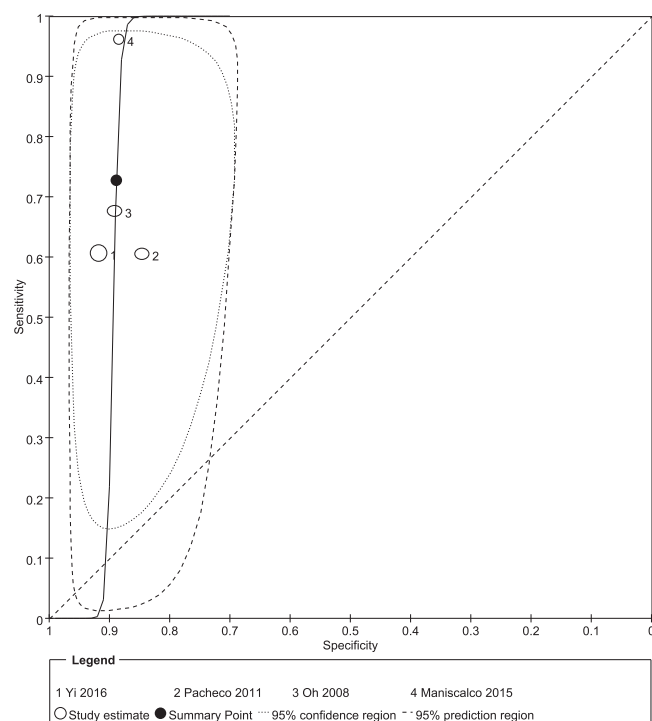


FIG 3. A, HSROC curve on the diagnostic utility of FENO measurement for predicting CVA in 10 studies of patients with chronic cough (defined by cough for ≥ 8 weeks). **B-D**, Subgroup analyses in 7 studies with a prospective design (Fig 3, B), 7 studies with guideline-based diagnostic criteria for CVA (Fig 3, C), and 6 studies that meet the diagnostic recommendations in international guidelines (using normal chest x-rays and guideline-based diagnostic criteria for CVA; Fig 3, D).^{5,6} The size of the circle is proportionate to the size of the study. Summary point indicates summary values for sensitivity and specificity. A 95% prediction region is the confidence region for a forecast of the true sensitivity and specificity in future studies. The HSROC curve is truncated outside of the area for which data points exist.

TABLE I. Summary of meta-analyses by RQ

No. of studies	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	Summary AUC (95% CI)	Diagnostic OR (95% CI)	I^2 (95% CI)
RQ1. FENO to predict CVA (in cough ≥ 8 wk)							
10	0.72 (0.61-0.81)	0.85 (0.81-0.88)	4.7 (3.6-6.2)	0.33 (0.23-0.47)	0.87 (0.83-0.89)	14 (8-26)	94 (89-99)
RQ2. FENO to predict either CVA or EB							
4	0.73 (0.53-0.86)	0.89 (0.84-0.92)	6.5 (4.3-9.8)	0.31 (0.16-0.58)	0.89 (0.86-0.92)	21 (8-54)	44 (0-100)
RQ3. FENO to predict nonasthmatic EB							
4	0.72 (0.62-0.80)	0.83 (0.73-0.90)	4.1 (2.6-6.6)	0.34 (0.25-0.47)	0.81 (0.77-0.84)	12 (6-23)	0 (0-100)

**FIG 4.** HSROC curve on the diagnostic utility of FENO measurement for predicting either CVA or EB in 4 studies of patients with chronic cough.

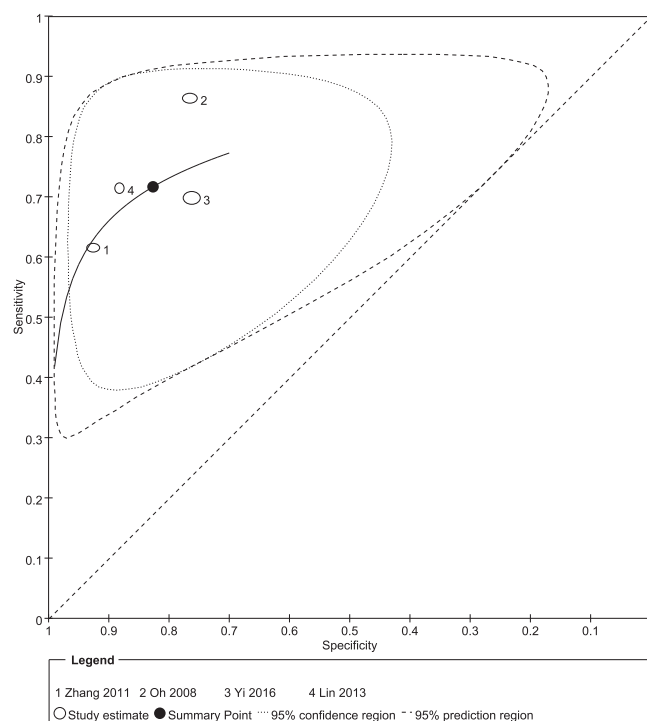
however, further analysis was not possible because of a small number of included studies.

RQ3: Diagnostic utility of FENO measurement for EB in nonasthmatic patients with chronic cough

Four studies of 390 nonasthmatic patients with chronic cough were analyzed (Fig 2, C).^{15,24,32,33} Optimal cutoff levels ranged from 22.5 to 31.7 ppb. Sensitivity was estimated as 0.72 (95% CI, 0.62-0.80; 95% prediction, 0.30-0.94; $I^2 = 3.6\%$), and specificity was estimated as 0.83 (95% CI, 0.73-0.90; 95% prediction, 0.17-0.99; $I^2 = 61.8\%$). In the HSROC curve analysis the summary AUC was calculated as 0.81 (95% CI, 0.77-0.84; Fig 5). A threshold effect was suggested by the appearance of the HSROC curve. However, further analysis for heterogeneity was not possible because of a small number of included studies.

DISCUSSION

FENO values can reflect T_H2 airway inflammation, which might help define the T_H2 endotype of chronic cough. Here we identified

**FIG 5.** HSROC curve on the diagnostic utility of FENO measurement for predicting EB in 4 studies of nonasthmatic patients with chronic cough.

the diagnostic potential of FENO measurement in predicting 2 major T_H2 inflammatory conditions underlying chronic cough: CVA and EB. We found that FENO measurements had moderate diagnostic accuracy in predicting CVA in adult patients with chronic cough. The estimated summary AUCs ranged from 0.81 to 0.89, according to the RQ, or in subgroup analyses. Sensitivities were highly variable across studies, ranging from 0.41 to 0.93; specificities were more consistent, ranging from 0.77 to 1.00.

A major outcome of the present study is that the performance characteristics and potential applicability of FENO tests were reviewed systematically for the first time in the particular population of chronic cough. The moderate diagnostic accuracy demonstrated here indicated that the FENO test alone is not sufficient to diagnose CVA in patients with chronic cough (RQ1). However, a moderate diagnostic accuracy does not necessarily indicate a lack of utility; our meta-analyses suggested the direction of application of FENO tests in that it showed a high diagnostic potential for consistency and accuracy as a rule-in test for CVA rather than a rule-out test. Subgroup analyses restricted

to the studies with prospective design or the guideline-based diagnostic criteria for CVA support our conclusion that high specificity is a potential strength of FENO measurement in the diagnosis of CVA. In turn, FENO measurement might not replace direct challenge tests, such as the methacholine inhalation test, because the latter has the advantage of high sensitivity and is useful to rule out current asthma (at a cutoff level of PC₂₀ >16 mg/mL).³⁸

We observed that the sensitivities of FENO measurement were lower in 2 RQ1 studies.^{26,34} Both studies had methodological concerns, including having a retrospective design or lacking chest x-rays in the selection criteria. Such limitations might have reduced the sensitivity of FENO measurement; however, the summary sensitivity estimates remained at or less than 0.80 in our sensitivity analyses, excluding those 2 studies, or in other subgroup analyses. Sensitivity also varied with several conditions (see Table E5). We speculate that the variable FENO sensitivity might be due to limitations in the diagnostic criteria for CVA.^{5,6} Results of spirometry are frequently normal in patients with chronic cough, and thus current clinical guidelines recommend methacholine inhalation challenge tests in the diagnosis of CVA.^{5,6} Negative AHR can help to exclude the diagnosis of CVA, but positive AHR is suggestive of, but not specific to, asthma.³⁸ Also, determination of a positive treatment response (without placebo control) might not preclude spontaneous resolution of cough. In this regard sensitivity is less likely to be a strength of FENO measurement in real-world settings.

Performance characteristics were similarly demonstrated in the pooled analyses for FENO values in predicting either CVA or EB (RQ2). The pooled sensitivity and specificity were 0.73 (95% CI, 0.53-0.86) and 0.89 (95% CI, 0.84-0.92), respectively. Indeed, this topic has more clinical relevance because EB is another clinical condition with good corticosteroid responsiveness,^{5,6} and thus evaluation for CVA alone has limited clinical value. However, only 4 studies were identified that were relevant to this topic. Thus further studies are needed to validate the diagnostic role of FENO measurement for this purpose. Based on RQ1 analyses, we hypothesize that the performance characteristics observed in RQ2 were largely due to CVA predictability. Indeed, among 15 studies, there was a considerable proportion of CVA, comprising 36.8% (interquartile range, 28.3% to 48.8%) of the study population.

The optimal cutoff levels to predict CVA, EB, or both were variable (RQ1 and RQ2), although they ranged within 30 and 40 ppb in most studies (Figs 3, A, and 4, A). The variability in optimal cutoff levels might be due to the clinical heterogeneity between studies, such as population characteristics, selection criteria, FENO measurement devices, or diagnostic procedures for target conditions. In this study we adjusted for threshold effects using random-effects model HSROC analyses.¹⁹ However, because of the limited number of included studies, heterogeneity could not be fully assessed. Considering the performance characteristics and diagnostic potential of FENO measurement, we suggest further studies to determine diagnostic performance at relatively high cutoff levels (eg, 30, 35, 40, or 50 ppb) or at a fixed specificity value (eg, 0.95).

Our second major finding was that the FENO test might not be precise enough to predict EB in nonasthmatic patients with chronic cough (RQ3). Our HSROC curve analyses suggested that neither sensitivity nor specificity was a potential advantage of FENO measurement in this clinical setting; the pooled

sensitivity and specificity were 0.72 (95% CI, 0.62-0.80) and 0.83 (95% CI, 0.73-0.90), respectively. Because our findings were based on a small number of studies with some variations in the diagnostic procedure (n = 4), further validation is needed in larger populations. However, it is notable that a recent study of asthmatic patients³⁹ indicated less utility of FENO measurement for predicting airway eosinophilia. In the recent meta-analysis by Korevaar et al,³⁹ FENO measurement showed moderate diagnostic accuracy but low sensitivity and specificity for detecting sputum eosinophilia ($\geq 3\%$ of induced sputum) in adult patients with asthma; the summary AUC was 0.74 (95% CI, 0.70-0.78), and the pooled sensitivity and specificity were 0.66 (95% CI, 0.57-0.75) and 0.76 (95% CI, 0.65-0.85), respectively. The regulatory mechanism of FENO values might be distinct from that of sputum eosinophilia,¹² as suggested in clinical trials of mepolizumab (anti-IL-5 mAb) in patients with severe asthma.^{40,41} These findings indicate that FENO measurement might not fully replace induced sputum analyses. Also, we suggest that these findings collectively challenge the statement in the current American Thoracic Society guidelines,¹³ which strongly recommends use of FENO measurement in the diagnosis of eosinophilic airway inflammation.

However, the clinical utility of FENO should not be dismissed in the nonasthmatic population with cough. The induced sputum test has become the best proxy to define lower airway eosinophilia, but there have been concerns about its feasibility and reproducibility.⁴² Considering the historical background for developing the clinical concept of nonasthmatic EB (which was to identify corticosteroid-responsive patients among the nonasthmatic population with cough),⁴³ additional studies are needed to investigate the utility of FENO measurement in predicting inhaled corticosteroid responsiveness rather than predicting sputum eosinophilia. To the best of our knowledge, no studies have used validated cough measurement tools to examine such utility in nonasthmatic patients with chronic cough.¹⁷

Several major limitations need to be considered in interpreting our findings. First, heterogeneity could not be fully investigated because of the limited number of studies included. Several factors, such as demographics, selection criteria, clinical settings, FENO measurement device, and definitions of target conditions, might have contributed to the observed heterogeneity.

Second, the majority of studies included (10/15) were conducted in Asia, and 7 were published in Chinese-language journals. Thus issues can be raised about generalizability. We could not fully examine regional differences because the number of studies from Western populations was limited. However, specificity was comparable between Asian and Western regions (see Table E5).

Third, publication bias could not be determined because of the lack of techniques for detecting such biases in diagnostic test accuracy reviews.⁴⁴ However, publication bias was minimized by including the non-English literature, conference abstracts, and unpublished data.

Fourth, current diagnostic criteria for CVA might not be precise because (1) they are often based on positive AHR and might not preclude postviral cough⁴⁵ and (2) are premised on good clinical response to asthma therapy and might not encompass refractory asthma. However, CVA is generally considered to respond well to asthma treatment, and any heterogeneity of treatment response in patients with CVA has not been addressed yet. Collectively, the

present findings on CVA need to be interpreted cautiously and within the context of current clinical guidelines for chronic cough.^{5,6}

Finally, the possibility of overestimated diagnostic accuracy might be present; we tried to minimize this risk by excluding case-control studies and including unpublished data and the non-English literature in the process of study selection. However, all of our included studies were derivation studies, which could lead to overoptimistic estimations of sensitivity and specificity.¹⁸ However, we argue that this could be a paradoxical strength of the study because the diagnostic potential for its high specificity has not been reported previously in the chronic cough population.

These findings could help to develop a further validation study at a fixed cut-off (or specificity) level. These efforts could finally lead to the development of specific recommendations on the use of FENO measurement in clinical guidelines for patients with chronic cough.

In conclusion, the present systematic review and meta-analysis demonstrated overall moderate diagnostic accuracy of FENO measurement in predicting CVA, EB, or both in adult patients with chronic cough. Pooled analyses indicated the diagnostic potential of FENO measurement as a rule-in test for CVA. The number of studies on EB was small, but available evidence suggested that FENO measurement was less useful to predict EB in nonasthmatic patients with chronic cough. Further studies are necessary to validate the best ways to use the FENO test in patients with chronic cough.

We thank Professor Heikki Koskela (Kuopio University, Finland) for his advice on data analyses. Also, we thank Professor Krzysztof Kowal (Medical University of Białystok, Poland), Professor Mauro Maniscalco (Hospital S. Maria della Pietà, Italy), and Dr Stefano Pizzimenti (University of Torino, Italy) for providing the information on their study design. Finally, we thank Professor Mi-Jung Oh (Bundang Jaeseng Hospital, Korea) and Professor Dong-Chull Choi (Sungkyunkwan University, Korea) for providing the original data.

Key messages

- FENO measurement has moderate diagnostic accuracy for predicting CVA or EB in patients with chronic cough.
- Optimal diagnostic points obtained from individual studies showed that specificity is higher and more consistent than sensitivity in predicting CVA.

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