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Original Article

Accuracy of objective tests for diagnosing adult asthma in symptomatic patients: A systematic literature review and hierarchical Bayesian latent-class meta-analysis

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AHR, airway hyperresponsiveness;

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oxide; HSROC, hierarchical summary

receiver operating characteristic;

LR, likelihood rate; QUADAS-2, Quality

Assessment of Diagnostic Accuracy Studies-2

ABSTRACT

Background: We obtain summary estimates of the accuracy of additional objective tests for the diagnosis of adult asthma using systematic review and meta-analysis of diagnostic test accuracy studies.

Methods: Medline, Embase, and other relevant electronic databases were searched for papers published between January 1989 and December 2016. Studies were included if they evaluated the diagnostic accuracy of objective tests, including airway reversibility (AR), airway hyperresponsiveness (AHR), and fractionated exhaled nitric oxide (FeNO) for the diagnosis of adult asthma in patients with symptoms suggestive of asthma. If papers were assessed appropriate using the adapted QUADAS-2 tool, meta-analysis was conducted using the hierarchical bivariate model. This hierarchical model accounts for both within and between study variability.

Results: Sixteen studies reported the performance of the evaluated objective tests at presentation. For diagnosis of adult asthma, overall sensitivity and specificity for AR were 0.39 (95% confidence interval [CI] 0.18 to 0.66) and 0.95 (95% CI 0.86 to 1.00); for AHR, 0.86 (95% CI 0.61 to 1.00) and 0.95 (95% CI 0.77 to 1.00); for FeNO, 0.65 (95% CI 0.53 to 0.77) and 0.83 (95% CI 0.75 to 0.90). Comprehensive comparison of three diagnostic tools for adult asthma using the back-calculated likelihood rate (LR) showed that AR and AHR corresponded to a higher LR+, and AHR gave a lower LR-.

Conclusions: In the current situation of no gold standard for diagnosis of adult asthma, AR and AHR are appropriate for ruling-in the true diagnosis, and AHR is superior for ruling-out a diagnosis. Since each objective test had a specific characteristic, it should be chosen depending on the situation, such as the capacity of the institution and the conditions of patients.

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Introduction

Asthma is a common chronic respiratory disease characterized by paroxysmal or persistent respiratory symptoms associated with variable airflow obstruction, airway hyperresponsiveness (AHR) and an underlying inflammation.^{1,2} As it is a heterogeneous disease with a variety of symptoms, including wheezing, cough, shortness of breath, and chest tightness, there is no single symptom to define asthma. And also, it is difficult to be certain of the diagnosis of asthma based upon history alone, because the

symptoms of asthma are also seen in several other respiratory diseases.^{3–5} Some studies indicate that 30% of patients with a physician diagnosis of asthma are misdiagnosed.^{6–12} Asthma may mimic other common conditions and may be either over-diagnosed¹³ or under-diagnosed.¹⁴

Physiologically, asthma is characterized by airway reversibility (AR) to β_2 -agonists and/or AHR. It is well known that tests of AR has high specificity and low sensitivity for diagnosing asthma due to many patients with asthma having a normal or near-normal lung function,^{15–17} and in these cases, bronchial challenge testing is recommended to confirm the presence of the disease. In contrast, tests of AHR are very sensitive for determining an asthma diagnosis but are not very specific because AHR is not unique to asthma, and patients with other diseases, such as allergic rhinitis, can have AHR without asthma.¹⁸

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Pathologically, eosinophilic airway inflammation is a key pathological feature of asthma. The test of fractional exhaled nitric oxide (FeNO) is simple, convenient and non-invasive in evaluating eosinophilic airway inflammation.¹⁹ According to systematic reviews,^{20,21} FeNO was 65–72% overall sensitive, and 78–82% overall specific in the meta-analysis for making a diagnosis of asthma. However, asthma is a heterogeneous disorder having various subtypes of airway inflammation.^{22–24} It was noted that non eosinophilic asthma is common, accounting for 22–55%.^{25–27}

One reason so many people are misdiagnosed is that there is no standard test for asthma. The best objective tests for diagnosing adult asthma, including bronchial challenge tests, in unselected asthma patients in a real-world situation, has yet to be demonstrated. The aim of the present study was to evaluate the different diagnostic tools and to determine the best strategy for applying these tests in a real-world situation.

Methods

Data sources and search strategy

We searched several databases (Pubmed, EMBASE, and Web of Science) for relevant prospective studies published between January 1989 and December 2016. “reversibility”, “hyper-responsiveness”, or “exhaled nitric oxide”, combined with “asthma”, “sensitivity”, and “specificity” were key words used for searching. Moreover, reviews and references lists of relevant article were screened for additional articles of interest. The searches were conducted independently by two authors.

Inclusion and exclusion criteria

Studies were included if they met the following criteria: (1) prospective diagnostic test study design; (2) diagnostic accuracy evaluation of objective tests compared with conventional criteria; (3) sufficient data to reconstruct a 2×2 contingency table for meta-analysis; and (4) eligible patients with symptoms suggestive of asthma. Studies were excluded if one of the following existed: (1) case reports, editorials, reviews and abstracts; (2) case-control or retrospective study designs; and (3) childhood asthma. Two reviewers independently screened all the studies for suitability for inclusion. Disagreements were resolved according to the opinion of a third author. Study selection is summarized in Figure 1.

Data extraction and synthesis

Our pre-defined primary outcomes included first author, country, year of publication, sample size, age, diagnostic standard for asthma, sensitivity, specificity and numbers required for reconstruction of a 2×2 table (true positive, false negative, false positive and true negative). When pertinent data were not included in a published article, the corresponding author was contacted. If a response was not provided, the article was excluded.

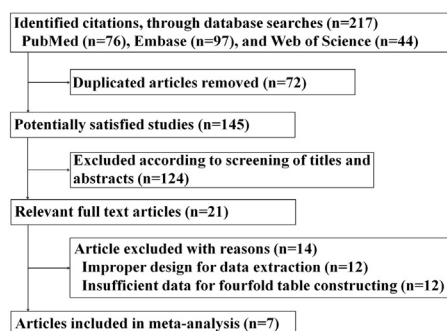
Quality assessment

The quality of each included studies was assessed with the criteria in the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool,²⁸ that evaluates the risk of bias and applicability of diagnostic accuracy studies. It consists of four key domains: patient selection, index test, reference standard, flow and timing. Each is assessed in terms of risk of bias and the first three in terms of issues regarding applicability.

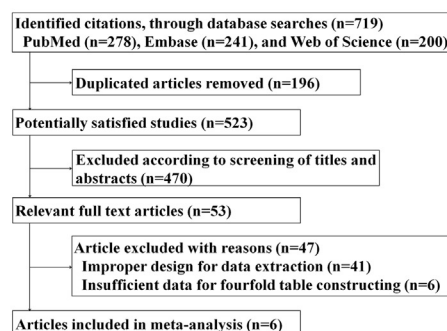
Statistical analysis

We tabulated 2×2 contingency tables, which included true positives (a), false positives (b), false negatives (c), and true negatives (d). Sensitivity ($a/(a+c)$), specificity ($d/(b+d)$) with corresponding 95% confidence interval [CI] were calculated. We used a Bayesian hierarchical model adjusting for the imperfect nature of the reference standard in a bivariate meta-analysis of diagnostic test sensitivity and specificity. The model allows for various reference standards to be used in individual studies, a feature commonly encountered when a gold standard reference is either nonexistent or prohibitive. As lack of a gold standard reference test is an acknowledged problem in studies of asthma diagnostics, we used the hierarchical summary receiver operating characteristic (HSROC) that it models the variation in diagnostic accuracy and cut-off values, both well-recognized sources of heterogeneity across diagnostic studies.²⁹ A recent statistical package, the hierarchical summary receiver-operating characteristic (HSROC) has been proposed to optimize the realization of meta-analyses on the accuracy of diagnostic tests with an imperfect standard. This statistical approach enables the calculation of pooled estimates of the sensitivity and specificity of a test and provides a mechanism to provide more precise estimates of the diagnostic accuracy of different imaging methods.

(a) Airway reversibility (AR)



(b) Airway hyperresponsiveness (AHR)



(c) Fractionated exhaled nitric oxide (FeNO)

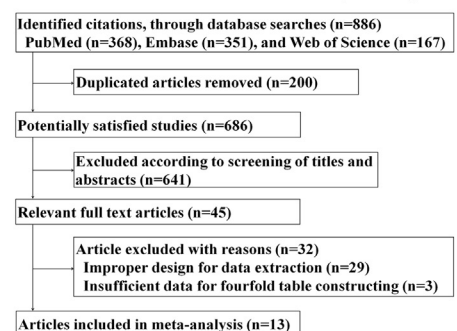


Fig. 1. Flow chart of study selection for inclusion in the systemic review.

Calculation of LR_s and Bayes theorem

Likelihood ratios (LRs) are basically a ratio of the probability that a test result is correct to the probability that the test result is incorrect. The sensitivity and specificity of the test are the numbers used to generate a LR, which is back-calculated for both positive and negative test results and is expressed as 'LR+' and 'LR-', respectively. The calculations are based on the following formulas:

$$LR+ = \text{sensitivity}/1 - \text{specificity}$$

$$LR- = 1 - \text{sensitivity}/\text{specificity}$$

LRs have unique properties that make them particularly useful for clinicians decision-makers. The LR + corresponds to the clinical concept of "ruling-in disease" for higher LR+ and "ruling-out disease" for lower LR-. A good diagnostic test has typically LR + greater than 5.0 and LR-less than 0.2.³⁰

Table 1
Characteristics of included studies.

First author and year	Sample size	Age*	%Female	%FEV ₁ *	Diagnostic standard	TP	FN	FP	TN	Sensitivity (%)	Specificity (%)
(a) Airway reversibility (AR)											
Backer (2015) ³⁵	190	31.9 ± 13	64%	95 ± 17	Reversibility of FEV ₁ , PEF variation and AHR to methacholine or mannitol	16	106	5	63	13.1	92.6
Tomita (2013) ³⁶	566	49 (18–88)	57.6%	84.4 (24.0–121.7)	Reversibility of FEV ₁ and/or AHR to methacholine	59	308	2	197	16.1	99.0
Cordeiro (2011) ³⁷	113	39 (7–83)	67%	n/a	Symptoms, reversibility of FEV ₁ , and AHR to histamine	23	18	2	70	56.1	97.2
Fortuna (2007) ³⁸	50	37 (18–68)	50%	99 ± 10	AHR to methacholine	17	5	4	24	77.3	85.7
Yurdakul (2005) ¹⁸	123	36.6 ± 10.7	71.7%	86.6 ± 17.6	Reversibility of FEV ₁ or PEF, AHR to methacholine, and/or PEF variation	19	41	3	60	31.7	95.2
Smith (2004) ³⁹	47	41.6 (9–72)	47%	90.5 ± 18.4	Reversibility of FEV ₁ and AHR to hypertonic saline	7	10	0	30	41.2	100
Hunter (2002) ⁴⁰	110	44 (15–70)	49%	85.0 ± 1.7	Reversibility of FEV ₁ , PEF variation and AHR to methacholine	34	35	12	29	49.3	707
(b) Airway hyperresponsiveness (AHR)											
Backer (2015) ³⁵	190	31.9 ± 13	64%	95 ± 17	Reversibility of FEV ₁ , PEF variation and AHR to methacholine or mannitol	79	43	29	39	64.8	57.4
Yurdakul (2005) ¹⁸	123	36.6 ± 10.7	71.7%	86.6 ± 17.6	Reversibility of FEV ₁ or PEF, AHR to methacholine, and/or PEF variation	58	2	14	49	96.7	77.8
Berkman (2005) ⁴¹	85	21.9 ± 1.6	67%	91.9 ± 1.6	Patient history only three or more episodes of doctor recorded wheezing, dyspnoea or cough relieved by bronchodilators	35	5	6	39	85.0	87.5
Smith (2004) ³⁹	47	41.6 (9–72)	47%	90.5 ± 18.4	Reversibility of FEV ₁ and AHR to hypertonic saline	15	2	0	30	88.2	100
Hunter (2002) ⁴⁰	110	44 (15–70)	49%	85.0 ± 1.7	Reversibility of FEV ₁ , PEF variation and AHR to methacholine	63	6	4	37	91.3	90.2
Hedman (1998) ⁴²	230	44.0 ± 16.0	56%	85.5 ± 14.8	Reversibility of FEV ₁ or PEF, PFER variation, and/or AHR to a specific allergen or an exercise	47	14	30	139	77.0	82.2
(c) Fractionated exhaled nitric oxide (FeNO)											
Wang (2015) ⁴³	408	41	57.6%	n/a	Reversibility of FEV ₁ and/or AHR to methacholine	91	34	71	212	72.8	74.9
Schneider (2013) ⁴⁴	179	40.5 ± 15.4	59.1%	101.3 ± 17	Reversibility of FEV ₁ and/or AHR to methacholine	75	79	60	179	48.7	74.9
Tomita (2013) ³⁶	566	49 (18–88)	65%	84.4 (24.0–121.7)	Reversibility of FEV ₁ and/or AHR to methacholine	194	173	82	117	52.9	58.8
Schleich (2012) ⁴⁵	174	38 ± 18	60%	95 ± 14	AHR to methacholine	29	53	5	87	35.4	94.6
Cordeiro (2011) ³⁷	114	39 (7–83)	67%	n/a	Symptoms, reversibility of FEV ₁ , and AHR to histamine	33	9	6	66	78.6	91.7
Fukuhara (2011) ⁴⁶	61	54.8 (50.0–59.7)	48%	95.8	Reversible of FEV ₁ , AHR, airway sputum Eo (>=3%), at least two	33	9	2	17	78.6	91.7
Pedrosa (2010) ⁴⁷	114	36.5 ± 14.6	54.3%	97.91 ± 15	Symptoms and AHR to methacholine	26	9	22	57	74.3	72.2
Schneider (2009) ⁴⁸	160	38.7 ± 15.1	58.7%	100 ± 12.2	Reversibility of FEV ₁ and/or AHR to methacholine	24	51	6	79	32.0	92.9
Kostikas (2008) ⁴⁹	149	21.6 ± 2.3	46%	83.8 ± 12.2	Symptoms, along with one of the following: reversibility of FEV ₁ , AHR to methacholine, or clinical and spirometric response to ICS	33	30	13	73	52.4	84.9
Fortuna (2007) ³⁸	50	37 (18–68)	50%	99 ± 10	AHR to methacholine	17	5	10	18	77.3	64.3
Berkman (2005) ⁴¹	85	21.9 ± 1.6	67%	91.9 ± 1.6	Patient history only (three or more episodes of doctor recorded wheezing, dyspnoea or cough relieved by bronchodilators)	33	7	5	40	82.5	88.9
Smith (2004) ³⁹	44	41.6 (9–72)	47%	90.5 ± 18.4	Reversibility of FEV ₁ and AHR to hypertonic saline	14	2	6	22	87.5	78.6
Dupont (2003) ⁵⁰	240	41 ± 17	52%	101 ± 14	Reversibility of FEV ₁ and/or AHR to histamine	111	49	8	72	69.4	90.0

* Data are shown as mean and S.D. or range.

Abbreviation: Eo, eosinophil; FEV₁, forced expiratory flow volume at 1 s; n/a, not applicable; PEF, peak expiratory flow; TP, true positive; FP, false positive; FN, false negative; TN, true negative.

We used Bayes theorem to estimate the post-test probability of adult asthma, by multiplying the pre-test odds by the likelihood ratio, where pre-test odds are calculated by dividing the pre-test probability (1 – pre-test probability). Then the post-test probability equals post-test odds divided by (1 + post-odds).³¹ We evaluated the pre-test probability of 30%^{32–34} versus corresponding post-test probabilities following LR + or LR- of objective tests, based on the summary sensitivity and specificity using Fagan plot analysis.³⁰

Results

Study identification and characteristics

Seven studies for AR,^{18,35–40} six for AHR^{18,35,39–42} and thirteen for FeNO^{36–39,41,43–50} were eligible for this meta-analysis. The flow chart and according exclusion reasons were summarized in Figure 1. The sample sizes ranged from 44 to 566, and total of 1,199 patients for AR, 785 for AHR and, 2,344 for FeNO were included. The detailed characteristics of the included studies are shown in Table 1. All of the studies include post-puberty adults, with three studies^{37,44,47} extending to school age onset. Regarding the severity of airway obstruction, 14 studies were restricted to mild to moderate severity, one⁵⁶ included some patients with severe airway obstruction, and two^{37,43} did not state the degree of airway obstruction.

Quality assessment

A quality assessment of the included studies was performed using QUADAS-2 criteria. Table 2 showed the quality assessment of individual studies.

Meta-analysis

The overall sensitivity were 0.39 (95% confidence interval [CI] 0.18 to 0.66) for AR, 0.86 (95% CI 0.61 to 1.00) for AHR, and 0.65 (95% CI 0.53 to 0.77) for FeNO, while the overall specificity was 0.95 (95% CI 0.86 to 1.00) for AR, 0.95 (95% CI 0.77 to 1.00) for AHR, and 0.83 (95% CI 0.75 to 0.90) for FeNO (Fig. 2). The HSROC curve is shown in Figure 3. When LR was back-calculated, the LR+ was 7.8 for AR, 17.2 for AHR, and 3.8 for FeNO, while the LR- was 0.64 for AR, 0.15 for AHR, and 0.42 for FeNO.

Bayes analysis

We evaluated the pre-test probability of 30%, which had previously reported,^{33–35} corresponding post-test probabilities following a “positive” or “negative” of each objective tests, based on the summary sensitivity and specificity using Fagan plot analysis.³² In Figure 4, the Fagan plot analysis suggested that AHR was very informative, with approximately 88% post-test probability of asthma following a “positive” test result when pre-test probability was 30%, while the test of FeNO was somewhat inferior to the others. On the other hand, AHR was the most useful to “rule-out” diagnosis with a 5% post-test probability of asthma, following a “negative” AHR result.

Discussion

The present meta-analysis reveals that the objective tests are helpful in the diagnosis of adult asthma in patients with symptoms suggestive of asthma. Each test of AR and AHR was more

Table 2

Risk assessment of reference standard, using QUADAS-2.

	Risk of Bias				Applicability Concerns			
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard	
(a) Airway reversibility (AR)								
Backer (2015) [35]	–	?	?	?	–	?	?	
Tomita (2013) [36]	–	–	–	?	–	–	–	
Cordeiro (2011) [37]	?	–	–	–	?	–	–	
Fortuna (2007) [38]	+	+	?	?	–	–	?	
Yurdakul (2005) [18]	?	–	?	?	?	–	?	
Smith (2004) [39]	+	–	?	?	–	–	–	
Hunter (2002) [40]	?	?	?	?	?	?	?	
(b) Airway hyperresponsiveness (AHR)								
Backer (2015) [35]	–	?	?	?	–	?	?	
Yurdakul (2005) [18]	?	–	?	?	?	–	?	
Berkman (2005) [41]	–	–	–	–	–	–	–	
Smith (2004) [39]	+	–	?	?	–	–	–	
Hunter (2002) [40]	?	?	?	?	?	?	?	
Hedman (1998) [42]	–	–	–	–	–	–	–	
(c) Fractionated exhaled nitric oxide (FeNO)								
Wang (2015) [43]	–	–	+	?	–	–	?	
Schneider (2013) [44]	+	–	+	–	–	–	?	
Tomita (2013) [36]	–	–	–	?	–	–	–	
Schleich (2012) [45]	–	–	–	–	–	–	–	
Cordeiro (2011) [37]	?	–	–	?	?	–	–	
Fukuhara (2011) [46]	?	+	?	?	–	–	?	
Pedrosa (2010) [47]	–	–	–	–	–	–	–	
Schneider (2009) [48]	+	–	+	?	–	–	?	
Kostikas (2008) [49]	–	–	–	?	–	–	–	
Fortuna (2007) [38]	+	+	?	?	–	–	?	
Berkman (2005) [41]	–	–	–	–	–	–	–	
Smith (2004) [39]	+	–	?	?	–	–	–	
Dupont (2003) [50]	–	–	–	?	–	–	–	

– High ? Unclear + Low

informative to “rule-in” diagnosis of adult asthma, and AHR was to “rule-out” diagnosis, but not FeNO. In our study, the sixteen studies were eligible and re-viewed, which were excluded any cohort studies, because the findings presented in this article address of positioning of objective tests for diagnosing adult asthma in a real-world of unselected population of patients with suspected asthma.

When performing a meta-analysis, study heterogeneity is a problem that can arise. The heterogeneity between the studies could well be explained by patient-population differences, including clinical heterogeneity such as age of onset, atopy and severity of airways obstruction. Another potential cause of heterogeneity may be the various criteria used for the reference standard, since there is no gold standard for diagnosis of adult asthma. A random-effects model is frequently used in a situation with patient-population differences between studies, but is not useful if there is no gold standard for diagnosis. We chose a Bayesian HSROC model to adjust for the imperfect nature of the reference standard, since this model takes into account within- and between-study variability, including clinical heterogeneity and the lack of a diagnostic gold standard.

For diagnosing asthma, pulmonary function tests are recommended to be performed according to international European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines.^{11,51} Our data suggest that 39% and 86% of patients with asthma shows positive test of AR and AHR, respectively, and 5% of

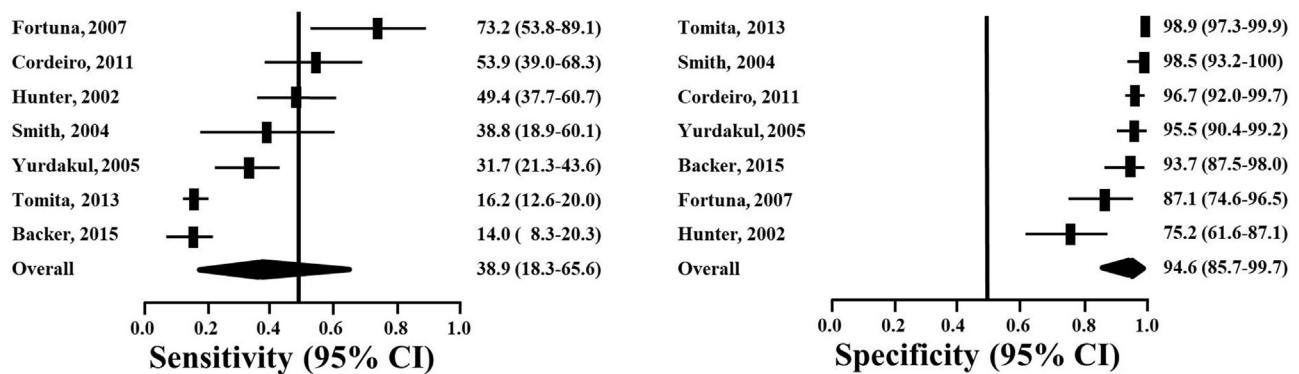
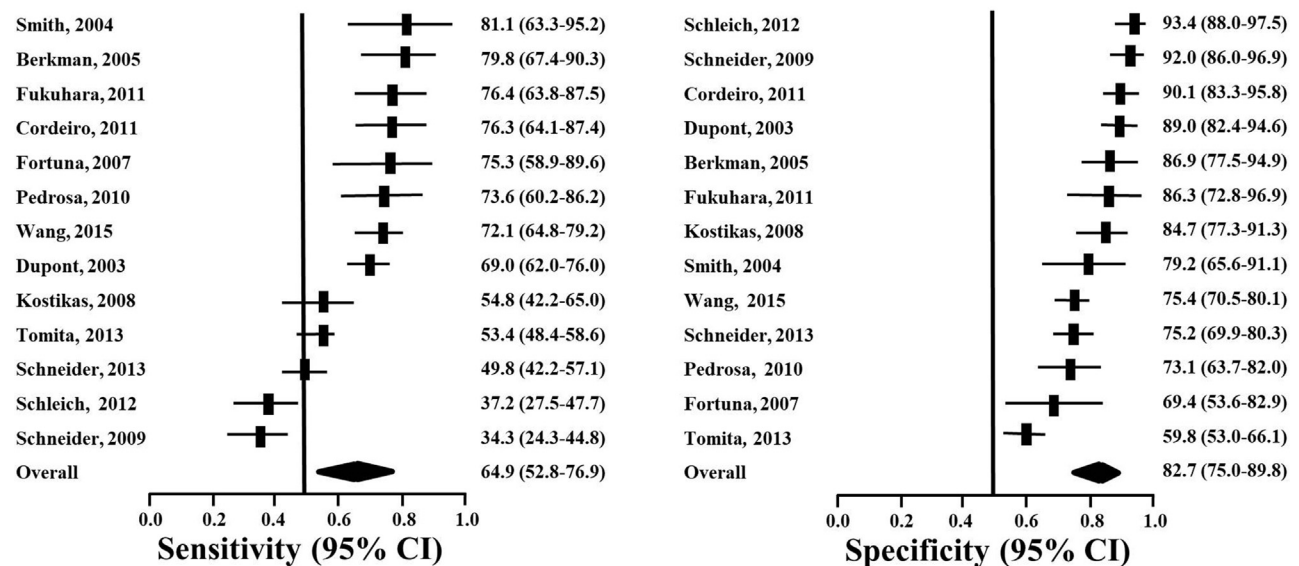
(a) Airway reversibility (AR)**(b) Airway hyperresponsiveness (AHR)****(c) Fractionated exhaled nitric oxide (FeNO)**

Fig. 2. Forest plot for sensitivity and specificity.

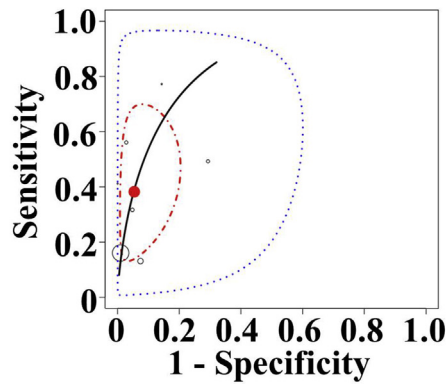
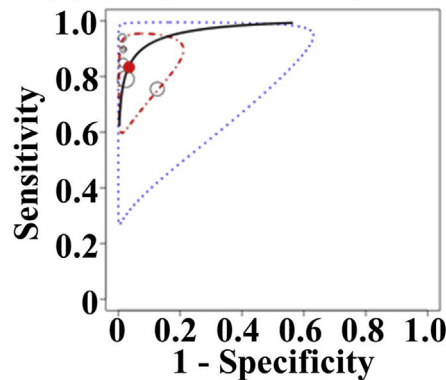
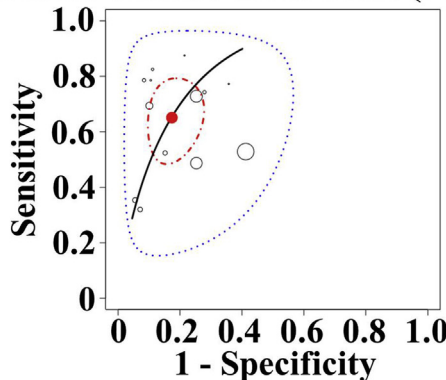
(a) Airway reversibility (AR)**(b) Airway hyperresponsiveness (AHR)****(c) Fractionated exhaled nitric oxide (FeNO)**

Fig. 3. Hierarchical summary receiver operating characteristic (HSROC) curves for diagnosing adult asthma. Pooled sensitivity and specificity as well as estimated summary receiver-operator characteristic (sROC) curves. The 95% confidence region (red dotted line) as well as the 95% prediction region (blue dotted line) are given.

patients without asthma has positive test of both AR and AHR. The traditional approach to the diagnosis of asthma like serial peak expiratory flows, spirometry, response to inhaled bronchodilator or a trial of corticosteroid are primarily based on demonstrating abnormal airway physiology, which may often not be present in mild asthma, hence the sensitivity of these tests is low.³⁹ In our study, we confirmed that each test of AR and AHR is most useful “rule-in” test for diagnosing asthma, because they showed highest LR + value. It was reported repeated measurement of AR contributed to develop the sensitivity of AR.² However, many patients with severe asthma do not have AR,⁵² and including AR as a diagnostic

criterion may sometimes cause under-diagnosis, which could have fatal consequences. Future work will be required for effectiveness of repeated measurement of AR.

In our study, we analyzed overall of sensitivity and specificity of AHR, which included different methods such as direct (methacholine or histamine), and indirect (exercise, dry air hyperpnea, distilled water, hypertonic saline, mannitol, and adenosine monophosphate) challenge. Direct challenge tests are sensitive for diagnosing asthma and indirect challenge tests are more specific in order to correlate better with eosinophilic airway inflammation.⁵³ We used the hierarchical summary receiver operating characteristic (HSROC) that it models the variation of challenge tests in diagnostic accuracy and cut-off values.

Our result was consistent with the report of Hunter and colleagues⁴⁰ indicated that methacholine responsiveness is more than twice as sensitive as AR for forced expiratory flow volume at one second (FEV₁) to diagnose asthma. The test of AHR is not so fully specific test and false-positive results are seen in patients with other diseases, including chronic obstructive pulmonary disease (COPD), allergic rhinitis and sarcoidosis.⁵⁴ In our study, we demonstrated that the test of AHR is more useful in “ruling-out” asthma (if the result is negative). A negative methacholine challenge test nearly always rules out asthma; however, a positive test result needs to be interpreted cautiously if the patient is not experiencing symptoms.^{55–57}

Asthma has been defined by the Expert Panel 3 of the National Asthma Education and Prevention Program as “a common chronic disorder of the airways that is complex and characterized by variable and recurring symptoms, airflow obstruction, AHR, and an underlying inflammation”.⁵⁸ Eosinophilic airway inflammation is one of key features of lung in patients with asthma. However, it can occur without AHR as in eosinophilic bronchitis and marked AHR can occur in the context of minimal airway eosinophils.⁵⁹ Our results of summary sensitivity and specificity of FeNO for diagnosing asthma is consistent with Kararasch and colleagues’ report²⁰ which demonstrated that in 25 reviewed studies with 4,518 participants, including cohort studies, overall sensitivity and specificity was 0.65 and 0.82, respectively. This study indicated higher diagnostic potential for ruling in than for ruling out the diagnosis of asthma due to the higher overall specificity than sensitivity. However, in our study, as test of FeNO showed to be lower value of LR+, which was 5 or less, and higher LR-, which was 0.2 or more, it indicated that single tool of FeNO was not suitable for “rule-in” as well as “rule-out” for diagnosing asthma.

This meta-analysis was based on a rigorous literature search, which resulted in the inclusion of 16 articles, and a validated appraisal tool was used to determine the risk of bias of included studies. Still, there are some limitations. With the statistical package used in the present study, we were able to calculate confidence and credible intervals for the overall sensitivity and specificity, but not for the LRs. No method was found to calculate CIs around the LRs that are derived from overall estimates of sensitivity and specificity. Other limitations include that there were recurrent sources of bias on three of the four items of the QUADAS 2 tool, which shows poor reporting of participants’ characteristics and study design for the included studies. Finally, we have no consideration as for sub-analysis of cut-off level of FeNO. Because a report of meta-analysis of FeNO demonstrated that characteristics of the subjects are the main sources of heterogeneity, but not cut-off level of FeNO.

We emphasize that diagnosis of asthma should be performed in combination of symptoms/physical findings/histories and objective tests. The triad of wheezing, cough, and shortness of breath contributes the major clinical feature of asthma, and one more of these

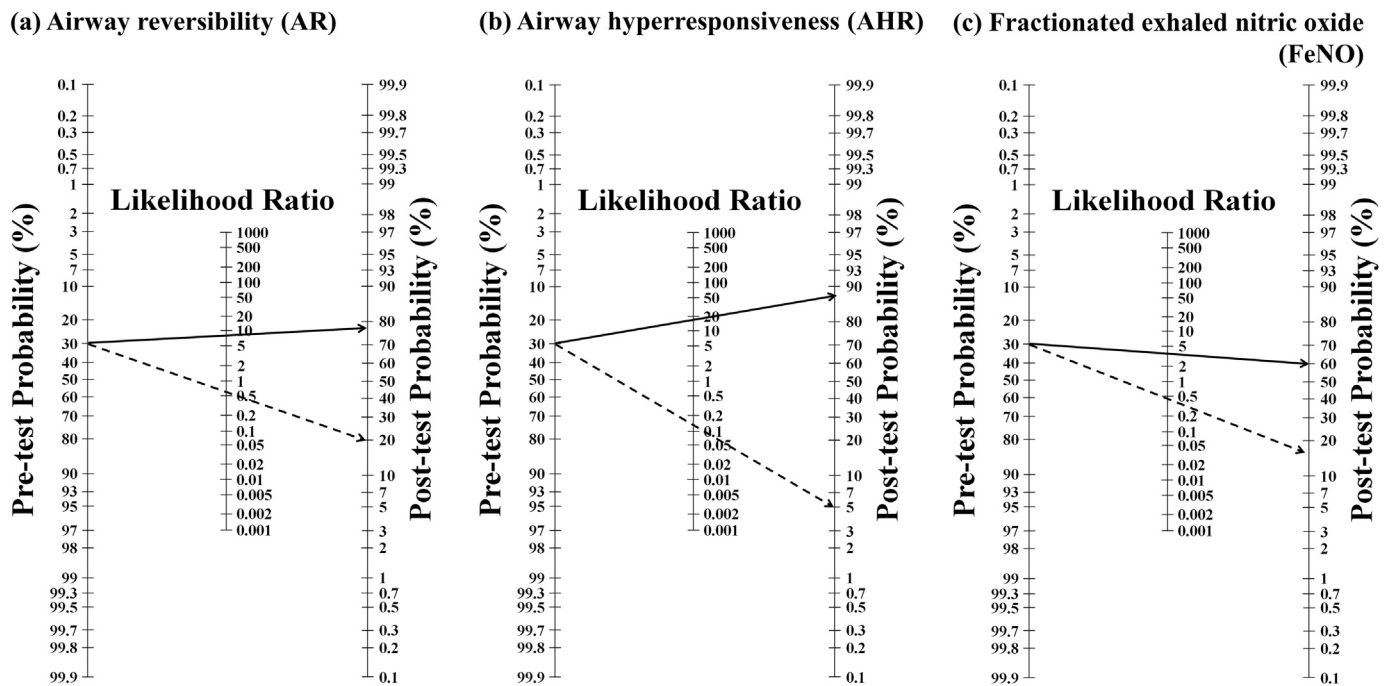


Fig. 4. Fagan plot analysis to evaluate the clinical utility of objective tests for diagnosing adult asthma. The Fagan plot consists of a vertical axis on the left with the pre-test probability, an axis in the middle representing the likelihood ratio (LR), and a vertical axis on the right representing the post-test probability. With pre-test probability of asthma of 30%, the post-test probability of asthma were obtained from positive and negative results of each objective test.

symptoms are reported by more than 90% of patients, but even this symptom complex is nonspecific.⁶⁰ We previously demonstrated that an integrated approach to diagnosis of asthma using symptom-sign scores could enhance the pre-test probability of having asthma.³⁶ Our results have no implication regarding the attributes of a FeNO test. The concept of heterogeneity occurs structurally in characterizing both the clinical presentation (phenotype) and underlying pathogenesis (endotype) of asthma. Clinical phenotypes and molecular endotypes are interrelated by genetic factors that play a key role in development of personalized approaches to diagnosis and treatment of asthma.^{61,62} Future work is required for personalized approaches to diagnosis of asthma using molecular endotypes. The National Institute for Health and Care Excellence (NICE) recommended that spirometry and FeNO testing were two mainstays of asthma diagnosis.³⁵ In this study, our results suggest that different combinations of objective tests, such as AR, AHR and FeNO, are needed to diagnose adult asthma with more accuracy, depending on situations such as the capacity of the institution and the conditions of patients. In the general physician setting, AR is required to least for diagnosing asthma in order to avoid overdiagnosis by a trial of corticosteroid. In the hospital/university settings, both AR and AHR are necessary in order to diagnose more accuracy.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

HS and KT had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. AS, SS, KN, ON, TI, and YT contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

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