Clinical utility of Th2-related markers for local allergic rhinitis: a meta-analysis and indirect comparison of diagnostic test accuracy

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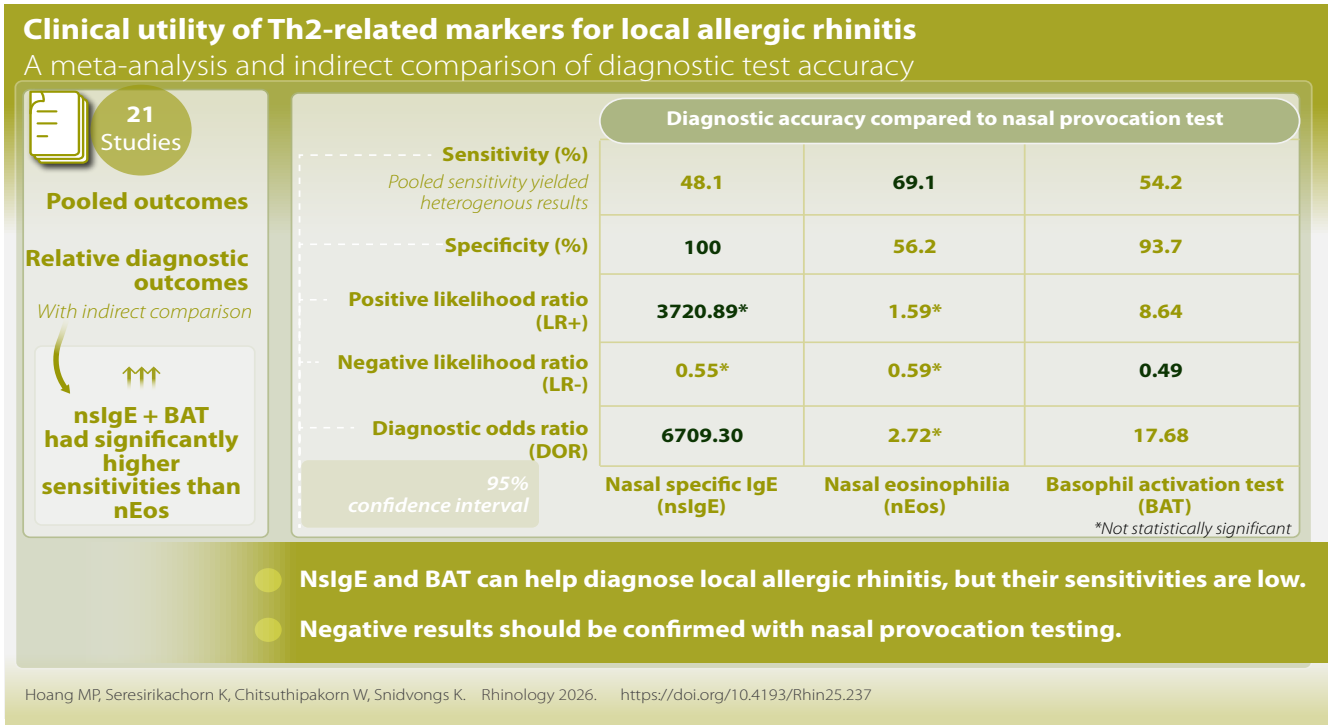

Abstract

Background: The role of Th2-related biomarkers as a diagnostic tool for local allergic rhinitis (LAR) remains controversial. This study seeks to assess the clinical utility of these markers and rank their diagnostic accuracy for LAR.

Methods: Systematic searches were conducted across five electronic databases. Pooled outcomes, including sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR-), and diagnostic odds ratio (DOR), were calculated. Relative diagnostic outcomes with a 95% confidence interval between index tests were computed using the indirect comparison of modalities.

Results: Twenty-one studies met the inclusion criteria, assessing the diagnostic accuracy of three index tests compared to nasal provocation test for LAR. Among the three biomarkers, sensitivities ranged from 48.1% to 69.1%, with nasal eosinophilia (nEos) showing the highest sensitivity but lowest specificity (56.2%). Nasal-specific IgE (nsIgE) demonstrated perfect specificity (100%) but limited sensitivity (48.1%), the highest DOR (significant), and the highest LR+ (not significant). Basophil activation test (BAT) had the lowest LR- with statistical significance. Indirect comparisons showed BAT and nsIgE had significantly higher sensitivities than nEos.

Conclusions: Nasal-specific IgE and the basophil activation test can help diagnose local allergic rhinitis, but their sensitivities are low. Negative results should be confirmed with a nasal provocation test. Heterogeneity in reported sensitivities further underscores the limitations of current diagnostic methods.

Key words: allergy, local allergic rhinitis, nasal specific IgE, basophil activation test, nasal eosinophilia, cytology

Introduction

Local allergic rhinitis (LAR) is a recently recognized phenotype of chronic rhinitis that has gained attention over the past decade. LAR is characterized by symptoms typical of allergic rhinitis (AR), a lack of positive results on systemic specific IgE (sIgE) tests, and a diagnosis confirmed through nasal provocation test (NPT) [1,2]. LAR locally demonstrates type 2 inflammation characteristics similar to AR after allergen exposure, featuring a Th2 and Th9 cytokine profile in the infiltration of mucosal cells along with positive NPT and nasal production of IgE, tryptase, and eosinophil cationic protein (ECP) [3-5]. Indirect evidence of a Th2 IgE-mediated inflammatory response is presented in LAR patients by a positive basophil activation test (BAT) response [1]. The similarities between LAR and AR have become more apparent following the successful treatment of LAR patients with allergen immunotherapy [6]. Therefore, a precise diagnosis is crucial to ensure that suspected patients receive appropriate treatment.

NPT is regarded as the gold-standard diagnostic tool for LAR by both the European Academy of Allergy and Clinical Immunology (EAACI) and the American Academy of Allergy Asthma and Immunology [7,8]. Reported NPT sensitivities range from 83.7% to 93.3% and specificities from 72.7% to 100% [9]. Diagnostic accuracy varies with interpretation methods: using VAS, sensitivity and specificity range from 38.5-100% and 86.4-100%; with TNSS, they are 93.3% and 77.4% [9]. When assessed by peak nasal inspiratory flow, acoustic rhinometry, or rhinomanometry, sensitivity and specificity range from 69.2-100% and 72.7-100% [9]. NPT settings differ across regions, especially regarding allergen availability, regulatory frameworks, and reimbursement policies [8]. The procedure requires skilled personnel and may necessitate prolonged hospital stays, limiting its widespread use [10]. Therefore, exploring alternative tests that are more patient-friendly and consume fewer resources is reasonable.

Besides clinical history and NPT, in vitro assays targeting the Th2 IgE-mediated inflammatory response are also helpful in confirming allergic phenotypes of rhinitis, including BAT and determination of inflammatory mediators (sIgE, eosinophil) at the local level [11]. However, the diagnostic accuracy of these tests for LAR remains uncertain despite their proposed inclusion in diagnostic algorithms as screening tools [8,11]. To address this, we conducted a systematic literature review and meta-analysis of current studies to evaluate the clinical utility of cytological and biological markers for LAR and rank their diagnostic accuracies.

Materials and methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered on PROSPERO under the ID number CRD42022296269 [12].

Eligibility criteria

A thorough literature search was performed across five electronic databases (PubMed, EMBASE, Web of Science, The Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov) from inception until May 10, 2024. Manual searches were performed for references in the included studies and other relevant sources. The detailed search strategy is described in Table S1 of the Supplement. Observational studies, including cohort, case-control, cross-sectional, and case series designs, involving patients of all ages with nonallergic rhinitis (NAR) were included if they reported the diagnostic accuracy of biomarkers for LAR and the corresponding 95% confidence intervals (CI). NAR is defined as the presence of rhinitis symptoms without systemic signs of allergic inflammation, such as sIgE in the blood or positive skin prick test (SPT) results [2]. The diagnostic criteria for LAR were based on negative SPT and serum sIgE with all allergens, and positive NPT with ≥1 allergen under NAR conditions [1,8]. Exclusion criteria were the study population with AR, chronic rhinosinusitis, acute rhinosinusitis, cystic fibrosis, and healthy condition. There was no limitation regarding language and meeting abstracts in which data could be extracted.

Study selection

Two reviewers (MH and KSe) independently screened titles and abstracts. The full texts of studies that passed the initial screening were then assessed for final eligibility. Any disagreements during the study selection process were resolved by the corresponding author (KSn).

Data extraction

Two review authors (MPH and WC) extracted data from eligible studies following the predetermined datasheet, including region, study design, population characteristics, features of index tests (cytological and biological markers) and standard test (NPT) for diagnosing LAR. The outcomes were sensitivity, specificity, diagnostic odds ratio (DOR), positive likelihood ratio (LR+), and negative likelihood ratio (LR-) of index tests.

Risk of bias assessment

The methodological quality of the included studies was evaluated using the updated Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [13]. A quantitative evaluation was performed using a scoring system for the QUADAS-2 tool, assigning 1 point for each 'low' risk of bias, 0 for 'high' risk, and 0.5 for 'unclear' risk, with a maximum possible score of 7 [14]. Two reviewers (MH and KSe) independently assessed the risk of bias for each item, categorizing them as low, high, or unclear. Any discrepancies were resolved by the corresponding author (KSn). Meta-regression was performed with the QUADAS-2 score as the continuous moderator to evaluate the impact of study quality on the diagnostic accuracy values of index tests.

Table 1. Characteristics of included studies.

Study	Country	Study design	No. of pt. (LAR/NLAR)	Age group	Index test	Allergen	Positive cut-offs for index tests	Positive index test n (%)	QUA-DAS-2 score
Rondon 2007 [19]	Spain	P	n=50 (27/23)	Adult	nsIgE	DP	≥0.35 kU/L	6 (22.0)	7
Rondon 2008 [20]	Spain	P	n=32 (20/12)	Adult	nsIgE	Grass, *Olea europea*	≥0.35 kU/L	7 (35.0)	7
Fuiano 2012 [21]	Italy	P	n=56 (30/6)	Children	nsIgE	*Alternaria*	≥0.35 kU/L	30 (100)	6.5
Gomez 2013 [22]	Spain	P	n=26 (16/10)	Adult	BAT	DP	SI≥2 and CD63$^+$ basophils ≥2.5%	8 (50.0)	5
Bozek 2015 [23]	Poland	P	n=46 (29/17)	Senior	nsIgE	DPa	≥0.35 kU/L	26 (89.6)	5
Refaat 2015 [24]	Egypt	P	n=40 (25/15)	Adult	nsIgE	Mixed	≥0.35 kU/L	16 (64.0)	2.5
Buntarickpornpan 2016 [25]	Thailand	P	n=54 (2/52)	Children	nsIgE	DP	≥0.35 kU/L	0 (0.0)	7
Krajewska-Wojtys 2016 [26]	Poland	P	n=53 (40/13)	Children	nsIgE	*Phleum* [a]	≥0.35 kU/L	38 (95.0)	6.5
Zicari 2016 [27]	Italy	P	n=18 (12/6)	Children	nsIgE	DP, DF, CD, LP	≥0.10 kU/L	12 (66.7)	6
					Nasal cytology		Nasal eosinophils >20% of total cells [b]	6 (50.0)	
Krajewska-Wojtys 2017 [28]	Poland	P	n=84 (21/63)	Adult	nsIgE	DP, *Alternaria*, Cat	≥0.35 kU/L	21 (100.0)	7
Tao 2018 [29]	China	P	n=12 (6/6)	Adult	nsIgE	DP	≥0.35 kU/L	2 (33.3)	2
Duarte Ferreira 2019 [30]	Portugal	R	n=20 (17/3)	Adult	nsIgE	DP, LD	≥0.35 kU/L	0 (0.0)	3.5
			n=17 (15/2) [c]		BAT		SI ≥2 and CD63$^+$ basophils ≥2.5%	8 (53.3)	
Meng 2019 [31]	China	P	n=73 (12/61)	Adult	nsIgE	DF	≥0.35 kU/L	11 (91.7)	7
Phothijindakul 2019 [32]	Thailand	P	n=48 (20/28)	Adult	Nasal cytology		Nasal eosinophils >20% of total cells [b]	16 (80.0)	6
Bozek 2020 [33]	Poland	P	n=47 (26/21)	Adult	nsIgE	Birch	≥0.10 kU/L	0 (0.0)	5.5
					BAT		SI ≥2 and CD63$^+$ basophils ≥15%	22 (84.6)	
Eckrich 2020 [34]	Germany	P	n=21 (0/21)	Adult	nsIgE	DP	≥0.35 kU/L	0 (0.0)	6
Santamaria 2020 [35]	Colombia	P	n=25 (7/18)	Adult	nsIgE	DP	≥0.12 kU/L	3 (42.9)	4
Tantilipikorn 2021 [36]	Thailand	P	n=62 (15/47)	Adult	nsIgE	DP	≥0.35 kU/L	0 (0.0)	6
Testera-Montes 2021 [37]	Spain	R	n=20 (10/10)	Adult	BAT	*Alternaria*	SI≥2 and CD63$^+$ basophils ≥2.5%	6 (60)	3.5
Gonzalez-Torres 2023 [38]	Spain	P	n=44 (7/37)	Children	BAT	DP, *Phleum*	SI≥2 and CD63$^+$ basophils ≥15%	1 (16.7) [d]	6
Testera-Montes 2025 [39]	Spain	P	n=38 (26/12)	Adult	BAT	DP, Grass, *Olea europea*	SI≥2 and CD63$^+$ basophils ≥2.5%	12 (46.2)	6.5

[a] Data on the most common local sensitization among patients with LAR can be extracted. [b] Positive cut-off for nasal eosinophilia. [c] BAT was only performed in 17 of 20 patients with LAR. [d] BAT was only performed in 6 of 7 patients with LAR. Abbreviations: LAR, local allergic rhinitis; NLAR, non-local allergic rhinitis; nsIgE, nasal specific IgE; BAT, basophil activation test; DP, *D. pteronyssinus*; DF, *D. farinae*; LD; *L. destructor*; CD, *C. dactylon*; LP; *L. perenne*; SI; stimulation index; P, prospective; R, retrospective.

Data synthesis and statistical analysis

Pairwise meta-analysis

We constructed 2x2 tables for the binary LAR outcome of each study to calculate diagnostic estimates for each index test. Data synthesis for any index test reported in at least two studies was performed using a bivariate mixed-effects model (Metadta package) [15]. The pooled sensitivity, specificity, LR+, LR-, and DOR for index tests were presented using a random-effects model. The

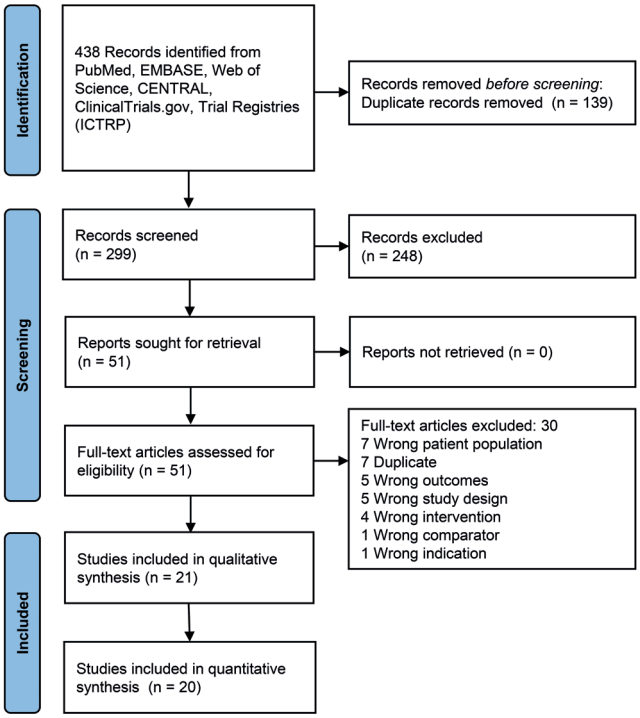

Figure 1. PRISMA flow chart.

sensitivity and specificity values between 90% and 100% indicate strong to excellent accuracy, while values ranging from 80% to 89% are considered moderately accurate and acceptable for diagnostic use [16]. The interpretation of LRs was conducted once statistical significance was achieved. LRs greater than 10 or less than 0.1 are generally regarded as providing strong evidence for confirming or excluding a diagnosis, respectively [17]. Forest plots for sensitivity and specificity were displayed as summary points with 95% CI. Summary receiver operating characteristic (SROC) curves and prediction contours were plotted to depict the summary operating point and confidence region. Publication bias was assessed using a Funnel plot and Deek's test, with a P-value less than 0.05 indicating significant asymmetry [18].

Subgroup analysis

We performed subgroup analysis to investigate heterogeneity and identify potential factors influencing diagnostic test accuracy. The potential covariates included study region (Europe, Asia, North America, South America, Africa), study design (prospective, retrospective), age group (adult, children), number of allergen concentrations used in NPT, criteria for a positive NPT (EAACI criteria, non-EAACI criteria) [7], positive cut-offs for the index tests, and biomarker collection techniques.

Sensitivity analysis

Sensitivity analyses involved repeating the primary meta-analysis after excluding studies identified as potential sources of heterogeneity using the Galbraith plot. Additionally, leave-one-out analysis was conducted to evaluate the impact of each individual study on the overall primary outcome estimates.

Indirect comparisons between competing diagnostic tests

The indirect comparison between index tests A and B was adjusted based on their direct comparisons with the standard test C (NPT). The log odds ratio for the adjusted indirect comparison between index tests A and B (lnORAB) was estimated using the formula lnORAB=lnORAC - lnORBC, with its variance calculated as Var(lnORAB)=Var(lnORAC) + Var(lnORBC) [19]. All analyses were performed using STATA 18.0 (StataCorp LP, College Station, TX, USA).

Results

Study selection

There were 438 potential abstracts initially retrieved for screening, with 50 full-text articles assessed for eligibility. Of these, 21 studies met the inclusion criteria and were included in the qualitative synthesis [20-40], while data from 20 studies were pooled for the meta-analysis [20-34,36-40]. Figure 1 presents the study selection flowchart following PRISMA guidelines.

Description of studies

A total of 869 participants, including 368 LAR patients, were analyzed in 21 studies. Among the 744 patients whose sex was reported, 426 were female. Mean age ranged from 8.9 to 68.5 years, with sample sizes varying between 12 and 84 patients. Table 1 summarizes the characteristics of the included studies. The studies focused on different age groups, with one study evaluating seniors [24], 15 assessing adults [20,21,23,25,29-38,40], and five focusing on children [22,26-28,39]. Studies were from 4 continents: Europe, Asia, Africa, and South America. Of the 21 studies, 20 had a prospective design, while only one used a retrospective design [31]. The diagnostic accuracy of three index tests for LAR was evaluated: nasal specific IgE (nsIgE), BAT, and nasal eosinophilia (nEos) on nasal cytology.

Evaluation of bias

Reference test, flow and timing contributed significant sources of bias (Figures S1-2 in the Supplement). Tao et al. used positive nsIgE as the diagnosis criterion for LAR instead of NPT [30]. Two studies exhibited a significant difference in the time interval between NPT, nsIgE, and BAT, introducing a potential timing bias [30,31]. The mean QUADAS-2 score was 5.5 out of 7 for studies using nsIgE and 6 out of 7 for both BAT and nEos (Table 1).

Nasal provocation test

Although NPT was utilized as the reference test in all included studies, the processing techniques differed across studies. Allergen extracts were used in single and serial dilutions, with different numbers of concentrations: 1 [24,27-30,34-36,38,40], 2 [33],

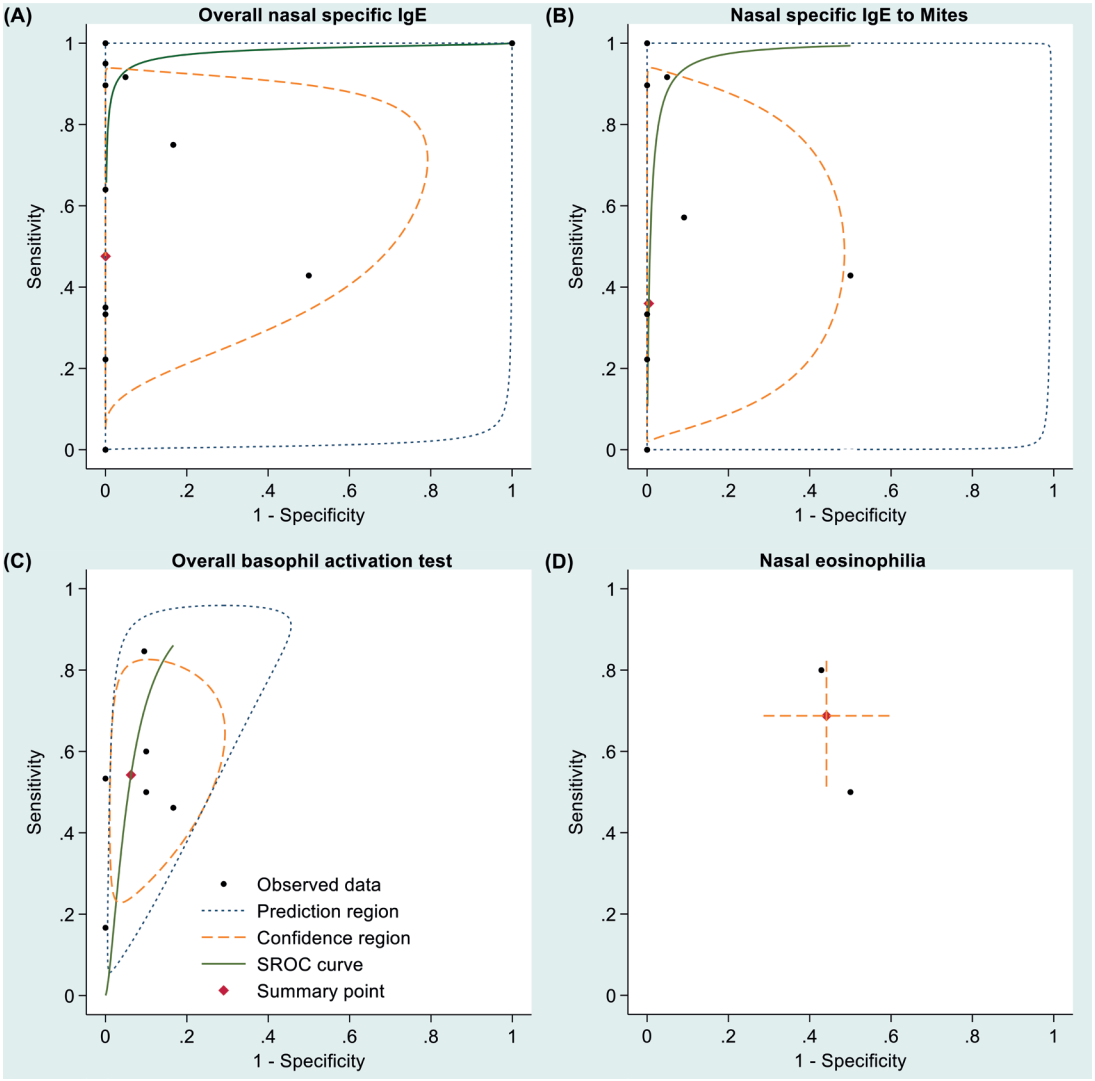

Figure 2. Summary receiver-operating characteristic curves of cytological and biological markers as surrogate methods for local allergic rhinitis detection: (A) overall nasal specific IgE; (B) nasal specific IgE to house dust mites; (C) overall basophil activation test; (D) nasal eosinophilia.

3 [20,23,26,31,37,39], 4 [21,32], and 5 [22]. The criteria for a positive NPT varied across studies due to diverse subjective and objective assessment tools and differing positivity cut-offs. Six studies did not adhere to the EAACI criteria for defining a positive NPT [25,26,30-32,37]. The characteristics of NPT in the included studies are summarized in Table S2 of the Supplement.

Diagnostic values of nsIgE

Sixteen studies assessed the diagnostic accuracy of nsIgE for LAR [20-22,24-32,34-37]. Fourteen studies applied a cut-off value of 0.35 kU/L [20-22,24-27,29-32,35-37], while the remaining two used a lower cut-off value of 0.1 kU/L [28,34]. Different nsIgE collection methods were described, including nasal lavage (Nacleiro method) [20,21,24-29,31,34,36,37], nasal packing [30,32,35], and paper disc (Marcucci method) [22]. Eckrich et al. [35] found no evidence of LAR in suspected patients with NAR when assessed using both NPT and nsIgE. Therefore, the pooled analysis of fifteen studies yielded an overall sensitivity of 48.1% (95% CI, 11.2%-87.3%) and specificity of 100% (95% CI, 77.4%-100%). The pooled estimates for LR+ and LR- were 3720.89 (95% CI, 0.25-5.49e+7) and 0.55 (95% CI, 0.01-31.11), respectively. Neither estimate reached statistical significance, as both were associated with p>0.05, and their 95% CIs spanned values both below and above 1. The pooled DOR was 6709.3 (95% CI, 1.92-2.35e+7) (Table 2, Figure 2, and Figure S3 in the Supplement).

Diagnostic values of nsIgE by allergen for LAR

Applying the categorization of allergens, the sensitivity and specificity of nsIgE to diagnose house dust mites (HDM)-driven LAR were 35.7% and 99.7%, respectively [20,24,26,28-32,36,37]. The sensitivity and specificity of nsIgE to diagnose other allergen-driven phenotypes were 99.9% and 99.7% for birch [24,27,34], 94.8% and 99.8% for *Alternaria* [22,24,29], and 86,7% and 100% for *Phleum* [24,27], respectively. When using mixed allergens, nsIgE identified

Table 2. Performance of cytological and biological markers in detecting local allergic rhinitis.

Test	Sensitivity (95% CI), %	Specificity (95% CI), %	LR+ (95% CI)	LR- (95% CI)	DOR (95% CI)
Overall nsIgE [a]	48.1 (11.2-87.3)	100 (77.4-100)	3720.89 (0.25-5.49e+7)	0.55 (0.01-31.11)	6709.30 (1.92-2.35e+7)
Overall BAT [b]	54.2 (36.3-71.1)	93.7 (85.1-97.5)	8.64 (3.66-20.37)	0.49 (0.33-0.72)	17.68 (6.43-48.63)
Neos [c]	69.1 (50.8-81.6)	56.2 (39.3-70.8)	1.59 (0.93-2.72)	0.59 (0.20-1.70)	2.72 (0.54-13.58)
P (nsIgE vs BAT)	0.85	0.37	0.23	0.85	0.30
P (nsIgE vs nEos)	0.40	<0.01	0.31	0.66	0.67
P (BAT vs nEos)	0.45	<0.01	0.37	0.75	0.42

[a] From 15 of analyzed studies [19-21,23-32,35,36]. [b] From 6 of analyzed studies [22,30,33,37-39]. [c] From 2 of analyzed studies [27,32]. Abbreviations: nsIgE, nasal specific IgE; BAT, basophil activation test; nEos, nasal eosinophilia; LR+, positive likelihood ratio; LR-, negative likelihood ratio; DOR, diagnostic odds ratio; CI, confidence interval.

Table 3. Performance of nasal specific IgE and basophil activation test by allergen in detecting local allergic rhinitis.

Type of allergen	No. of patient (No. of studies)	Sensitivity (95% CI), %	Specificity (95% CI), %	No. of patient (No. of studies)	Sensitivity (95% CI), %	Specificity (95% CI), %
		NsIgE			BAT	
Mites	444 (10)	35.7 (6.1-83.2)	99.7 (87.1-100)	66 (3)	48.2 (33.1- 61.7)	96.6 (75.8-99.2)
Birch	146 (3)	99.9 (0-100)	99.7 (60.1-100)	47 (1)	84.6 (64.9-95.6)	90.5 (69.6-98.8)
Alternaria	166 (3)	94.8 (78.7-98.6)	99.8 (0-100)	39 (2)	46.7 (26.1-70.8)	94.5 (73.5-99.3)
Phleum	99 (2)	86.7 (73.6-92.5)	99.5 (0-100)	NA	NA	NA
Olive tree	NA	NA	NA	16 (1)	75.0 (19.4-99.4)	91.7 (61.5-99.8)
Mixed	212 (5)	53.8 (5.2-96.1)	99.1 (59.7-100)	82 (2)	40.8 (24.5-58.1)	95.7 (85.4-99.4)

Abbreviations: nsIgE, nasal specific IgE; BAT, basophil activation test; CI, confidence interval; NA, not available.

LAR with an overall sensitivity of 53.8% and specificity of 99.5% (Table 3 and Figures S4-S8 in the Supplement) [21,25,28,29,31].

Subgroup analyses of nsIgE

Subgroup analyses showed that the nsIgE collection method and the number of allergen concentrations used in NPT significantly influenced both sensitivity and specificity of the test for diagnosing LAR (p<0.01). Additional factors affecting nsIgE sensitivity included study design (p<0.01) and age group (p=0.03), while specificity was influenced by region (p<0.01) and the criteria for a positive NPT (p=0.02) (Table 4).

Diagnostic values of BAT

Six studies assessed the diagnostic accuracy of BAT for LAR [23,31,34,38-40]. Four studies used a positivity cut-off for the BAT with a threshold of activated basophils ($CD63^+$ cells) set at ≥2.5% [23,31,38,40], while two studies applied a threshold of ≥15% [34,39]. In BAT, two studies used three allergen concentrations [23,39], one used four [34], and three used five [31,38,40]. The pooled analysis yielded an overall sensitivity of 54.2% (95% CI, 36.3%-71.1%) and an overall specificity of 93.7% (95% CI, 85.1%-97.5%). The pooled LR+ was 8.64 (95% CI, 3.66-20.37), the LR- was 0.49 (95% CI, 0.33-0.72), and the DOR was 17.68 (95% CI, 6.43-48.63) (Table 2, Figure 2, and Figure S9 in the Supplement). The utility of positive BAT to confirm LAR was moderate (LR+ 5- ≤10). The diagnostic value of BAT negativity to exclude LAR was low (LR- 0.2- <0.5). Both of these values were associated with p<0.05.

Diagnostic values of BAT by allergen for LAR

Applying the categorization of allergens, the sensitivity and specificity of BAT to diagnose HDM-driven LAR were 48.2% and 96.6%, respectively [23,31,40]. The sensitivity and specificity of BAT to diagnose other allergen-driven phenotypes were 84.6% and 90.5% for birch [34], 46.7% and 94.5% for *Altenaria* (38,40), and 75.0% and 91.2% for olive tree pollen [40]. When using mixed allergens, BAT identified LAR with an overall sensitivity of 40.8% and specificity of 95.7% (Table 3 and Figures S10-S12 in the Supplement) [39,40].

Subgroup analyses of BAT

Subgroup analyses showed that factors significantly affecting the sensitivity of BAT were the age group (p=0.02) and the number of allergen concentrations used in BAT (p<0.01). In contrast, no potential factors significantly influenced the specificity (Table 5).

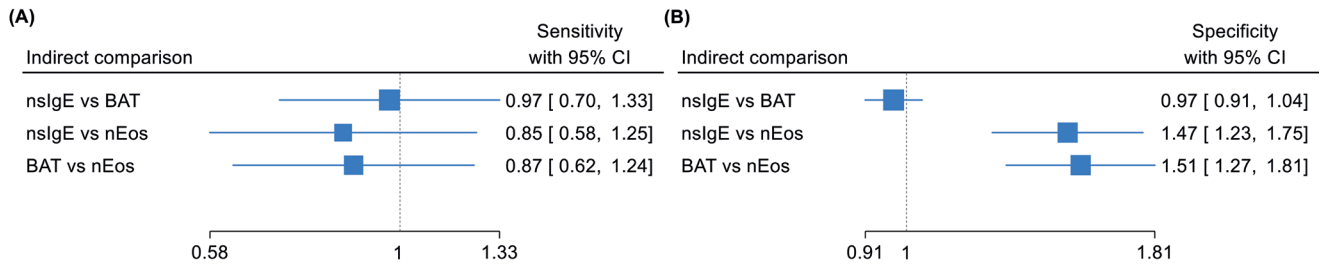

Figure 3. Sensitivity and specificity of indirect comparison. nsIgE, nasal specific IgE; BAT, basophil activation test; nEos, nasal eosinophilia.

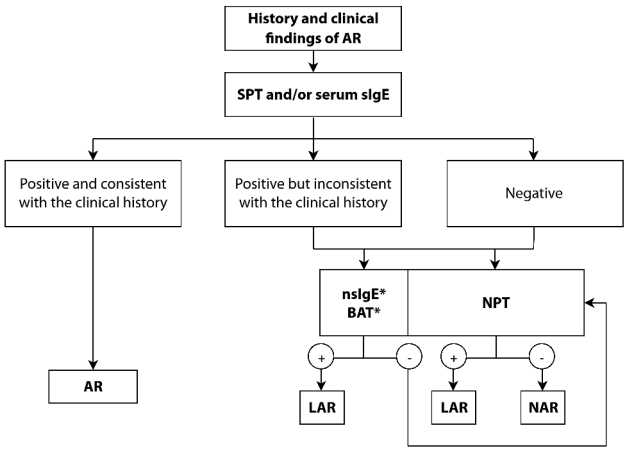

Figure 4. Clinical algorithm for diagnosing local allergic rhinitis. nsIgE, nasal specific IgE; BAT, basophil activation test; NPT, nasal provocation test; AR, allergic rhinitis; LAR local allergic rhinitis; NAR, nonallergic rhinitis; *, optional.

Diagnostic values of nEos

Two studies assessed the diagnostic accuracy of nEos on nasal cytology for LAR [28,33]. nEos was defined as nasal eosinophils accounting for >20% of the total cells collected from nasal scraping [28,33]. The pooled analysis yielded an overall sensitivity of 69.1% (95% CI, 50.8%-81.6%) and specificity of 56.2% (95% CI, 39.3%-70.8%). The pooled LR+ was 1.59 (95% CI, 0.93-2.72), the LR- was 0.59 (95% CI, 0.20-1.70), and the DOR was 2.72 (95% CI, 0.54-13.58) (Table 2, Figure 2, and Figure S13 in the Supplement). Neither estimate reached statistical significance, as they were associated with p>0.05, and their 95% CIs spanned values both below and above 1.

Diagnostic values of the combination of nsIgE and BAT

Only one study conducted simultaneous nsIgE and BAT measurements; however, uniformly negative nsIgE results precluded any meaningful evaluation of its diagnostic performance [31].

Meta-regression and evaluation of publication bias

Meta-regression analyses found no interaction between the QUADAS-2 score and the DOR of nsIgE (p=0.13) or BAT (p=0.75) in diagnosing LAR. Additionally, no evidence of publication bias was detected based on funnel plot asymmetry for the DOR of nsIgE (p=0.84) and BAT (p=0.93) (Figures S14-15 in the Supplement).

Sensitivity analysis

Galbraith plots identified only two studies [22,36] as potential sources of heterogeneity in the specificity of overall nsIgE for detecting LAR (Figures S16–S19 in the Supplement). Excluding these studies in the sensitivity analysis failed to substantially reduce heterogeneity in diagnostic estimates; however, the sensitivity of overall nsIgE decreased to 37.0% (95% CI, 7.0-81.0%) (Figure S20 in the Supplement). Furthermore, leave-one-out sensitivity analysis revealed that removing the study by Fuiano et al. [22] led to a significant increase in the specificity of overall nsIgE (Figures S21-24 in the Supplement).

Indirect comparisons between index tests

The relative sensitivity of nsIgE vs. BAT, nsIgE vs. nEos, and BAT vs. nEos were 0.97 (95% CI, 0.70-1.33), 0.85 (95% CI, 0.58-1.25), and 0.90 (95%CI, 0.74-1.10), respectively. No statistically significant differences were found between index tests (p>0.05), as shown in Table 2 and Figure 3.

The relative specificity of nsIgE vs. BAT, nsIgE vs. nEos, and BAT vs. nEos were 0.97 (95% CI, 0.91-1.04), 1.47 (95% CI, 1.3-1.75), and 1.51 (95% CI, 1.27-1.81), respectively. Both nsIgE and BAT demonstrated significantly higher specificity compared to nEos (p<0.01), as shown in Table 2 and Figure 3.

No significant differences were found in LR+, LR-, and DOR between index tests (p>0.05), as shown in Table 2.

Discussion

The challenge of NPT as the clinical diagnostic tool for LAR

NPT is a highly reliable diagnostic method for assessing clinical allergen reactivity, as it allows for the induction of localized allergic responses in a standardized and controlled environment [7,8]. Therefore, the test is considered the gold standard in accurately identifying LAR. However, NPT procedures are inconsistent regarding dosing regimens, methods of allergen application, and the criteria used to define a positive result [8]. Although considerable effort has been made to standardize the procedure through the proposal of a consensus protocol by EAACI [7], not

Table 4. Subgroup analysis of nasal specific IgE in detecting local allergic rhinitis.

Subgroup	No. of patient (No. of studies)	Sensitivity (95% CI), %	Specificity (95% CI), %
Region			
Europe	386 (9)	64.7 (7.8-97.6)	100 (0-100)
Asia	201 (4)	10.6 (0-91.2)	100 (69.3-100)
Africa	40 (1)	64.0 (42.5-82.0)	0.99 (78.2-100)
South America	25 (1)	42.9 (9.9-81.6)	50.0 (26.0-74.0)
P value		0.59	<0.01
Study design			
Prospective	632 (14)	57.5 (18.1-90.3)	100 (75.8-100)
Retrospective	20 (1)	0.1 (0-19.5)	99.0 (29.2-100)
P value		<0.01	0.75
Age group			
Adult	491 (11)	42.8 (15.3-72.1)	97.7 (95.2-100)
Children	161 (4)	81.1 (62.9-99.2)	71.5 (39.1-100)
P value		0.03	0.12
Positive cut-off for nsIgE			
≥0.35 kU/L	587 (13)	57.1 (15.2-90.7)	100 (0-100)
≥0.10 kU/L	65 (2)	23.7 (13.1-39.6)	95.7 (78.1-99.2)
P value		0.68	0.28
Method of collecting nsIgE sample			
Nasal lavage	531 (12)	31.2 (4.7-80.3)	100 (50.0-100)
Paper disc	36 (1)	100 (88.4-100)	0 (0-45.8)
Nasal packing	85 (2)	72.1 (47.5-88.1)	95.7 (87.2-99.4)
P value		<0.01	<0.01
No. of allergen concentrations used in NPT (n)			
1	325 (8)	69.1 (25.2-93.8)	100 (70.5-100)
3	186 (4)	5.9 (0-15.6)	99.0 (96.8-100)
4	105 (2)	55.5 (37.9-74.2)	96.0 (88.6-99.2)
5	36 (1)	99.0 (88.4-100)	0.1 (0-45.9)
P value		<0.01	<0.01
Criteria of positive NPT			
EAACI criteria	391 (9)	76.2 (25.1-96.7)	100 (3.9-100)
Non-EAACI criteria	261 (6)	10.2 (0-78.7)	100 (58.5-100)
P value		0.18	0.02

Abbreviations: nsIgE, nasal specific IgE; NPT, nasal provocation test; EAACI, European Academy of Allergy and Clinical Immunology; CI, confidence interval.

Table 5. Subgroup analysis of basophil activation test in detecting local allergic rhinitis.

Subgroup	No. of patient (No. of studies)	Sensitivity (95% CI), %	Specificity (95% CI), %
Study design			
Prospective	175 (5)	53.7 (31.7-74.4)	93.5 (84.3-97.5)
Retrospective	17 (1)	53.3 (26.6-78.7)	100 (15.8-100)
P value		1.00	0.93
Age group			
Adult	148 (5)	60.2 (44.6-73.8)	88.8 (76.9-94.9)
Children	44 (1)	16.7 (0.4-64.1)	100 (90.5-100)
P value		0.02	0.08
Positive cut-off for BAT			
SI≥2 + basophils ≥2.5%	101 (4)	51.2 (39.4-61.6)	88.4 (72.7-96.1)
SI≥2 + basophils ≥15%	91 (2)	72.1 (53.9-85.3)	97.2 (87.1-99.0)
P value		0.97	0.21
No. of allergen concentrations used in BAT (n)			
3	70 (2)	40.6 (23.2-61.9)	97.9 (85.9-100)
4	47 (1)	84.6 (65.1-95.6)	90.5 (69.6-98.8)
5	75 (3)	51.3 (37.9-63.7)	88.3 (68.2-95.7)
P value		<0.01	0.29
No. of allergen concentrations used in NPT (n)			
1	131 (4)	61.8 (42.9-77.6)	88.4 (76.2-94.7)
3	61 (2)	43.2 (23.7-63.8)	100 (0-100)
P value		0.24	0.07
Criteria of positive NPT			
EAACI criteria	175 (5)	53.7 (31.7-74.4)	93.5 (84.3-97.5)
Non-EAACI criteria	17 (1)	53.3 (26.6-78.7)	100 (15.8-100)
P value		1.00	0.93

Abbreviations: BAT, basophil activation test; NPT, nasal provocation test; EAACI, European Academy of Allergy and Clinical Immunology; CI, confidence interval.

all studies have followed the same criteria. These inconsistencies contribute to discrepancies in LAR prevalence across different regions [26,41]. Subgroup analyses related to NPT in our study showed that the number of allergen concentrations used in the test and the EAACI criteria for positivity influenced the accuracy of nsIgE in diagnosing LAR. This underscored the importance of a consistent reference standard in diagnostic accuracy studies.

The screening role of biomarker tests for LAR

Compared to the NPT, the diagnostic accuracy of the three Th2-related markers for LAR exhibited distinct characteristics. Among these, nEos on nasal cytology demonstrated the highest sensitivity (69.1%), followed by BAT (54.2%) and nsIgE (48.1%). The infiltration of eosinophils on the nasal mucosa is detected during the late phase of an allergic reaction [35]. The number of nasal eosinophils strongly correlated with the severity of nasal symptoms in AR, highlighting the role of nEos as a biomarker of

AR [42]. Additionally, eosinophils function as allergen-presenting cells, promoting Th-cell responses and contributing to inflammation [43]. Rondon et al. [20] also observed comparable eosinophil levels in nasal lavage from both LAR and AR groups, indicating that nEos on cytology could potentially serve as a marker for LAR. However, like nsIgE and BAT, the pooled sensitivity of this test remained below 80%, indicating suboptimal reliability for screening purposes. Furthermore, its invasive nature and the risk of inducing nasal irritation limit its feasibility for routine clinical application.

The confirmation role of biomarker tests for LAR

Given the high specificity values over 90%, both nasal specific IgE and BAT are recommended as confirmation tests for LAR. The scope of nsIgE assessment is based on the local production of sIgE in the nasal secretion of patients with negative skin tests after undergoing NPT [44]. A local increase in IgE production and class switch recombination to IgE was observed in the nasal and bronchial mucosa of both atopic and nonatopic patients with rhinitis [45] and asthma [46]. The pooled data suggested that nsIgE positivity could confirm the presence of LAR; however, the wide 95% CI of DOR and non-significant pooled LR+ and LR- values compromised the reliability of its accuracy.

Peripheral basophils play a significant role in allergic reactions, particularly in immediate IgE-mediated responses [47]. Locally produced IgE can circulate in the bloodstream and bind to FcεRI receptors on basophils, resulting in a positive BAT [48]. Although BAT showed slightly lower specificity compared to nsIgE, its significantly pooled LR+, LR-, and narrower 95% CI for DOR suggested greater reliability and consistency in confirming LAR.

In contrast, nEos is not useful for confirming LAR, as it showed very low specificity (56.2%) along with non-significant pooled LR+, LR-, and DOR. This result was consistent with the fact that nEos can also be present in other allergic [42] or nonallergic conditions [49].

Potential factors influencing the accuracy of the tests

Due to the evident discrepancy between nsIgE and positive NPT results, our study explored seven potential factors contributing to this variability, with subgroup analysis highlighting differences in nasal mucosa IgE sampling methods as a key contributing factor. These methods included in vitro detection of nsIgE using nasal lavage [20,21] and sinus packs [30,32], as well as in situ detection using paper discs [22]. These diverse approaches were identified as the primary reason for the low sensitivity of nsIgE detection in patients with positive NPT. Recently, Campo et al. [50] introduced a minimally invasive method for directly detecting nsIgE in patients with LAR using an automated immunoassay, reporting a sensitivity of 42.9%, which aligns with our results.

A substantial proportion of individuals with LAR experience symptom onset during childhood [8]. In the present study, nsIgE was detected more frequently in children with LAR than in adults. Accordingly, nsIgE-confirmed LAR should be considered a key differential diagnosis in the pediatric population and systematically excluded in children exhibiting typical AR symptoms but negative SPT or serum sIgE findings. In the current pediatric population, divergent findings have been reported, with an Asian study demonstrating low sensitivity [26] and European studies reporting high sensitivity [22,27,28]. Geographic subgroup analysis confirmed this pattern, showing that studies from Asia using mite allergens had low sensitivity [26,30,37], while those from Europe using pollen, grass, or fungi allergens had high sensitivity. House dust mites are common allergens in Asia [26].

Subgroup analysis revealed that the differences in allergen concentrations used in BAT affected the specificity of the test. Additionally, when analyzed by age, the sensitivity of BAT for diagnosing LAR was lower in children compared to adults. This could be due to a higher cut-off for BAT positivity used in the study involving children than those focused on adults [39]. %CD63$^+$ indicates the percentage of basophils with sIgE attached to the cell membrane [51]. In recent years, considerable efforts have been made to standardize the procedure, culminating in proposing a consensus protocol that defines a positive response as >5% CD63$^+$ basophils [52].

Clinical interpretation and future direction

NPT, however, is costly, requires specialized equipment, and is sometimes non-reimbursable [7,8]. BAT offers a less invasive, more comfortable, and less expensive alternative [52] and, together with nsIgE, may be used when standard allergy tests are inconclusive. Among the three index tests, nEos is the cheapest but has low diagnostic accuracy and is invasive. Our proposed clinical algorithm (Figure 4) integrates the findings of this study into practice.

Patients with LAR also exhibit local production of tryptase and eosinophilic cationic protein following NPT [3]. However, elevated nasal levels of these inflammatory mediators are not consistently detected, likely due to the limited sensitivity of current methods. Further exploration of localized mast cell activation in the nasal epithelium may offer future diagnostic value, with the key challenge being the development of reliable, non-invasive testing approaches.

Strengths and limitations

To date, there has been only one meta-analysis assessing the accuracy of nsIgE in diagnosing LAR. Rosalina et al. [53] extracted data from five studies and showed that nsIgE was a reliable diagnostic tool for HDM-driven LAR with an overall sensitivity of 90.0% and specificity of 96.0%. However, our findings demonstrated poorer diagnostic performance of nsIgE, with a sensitivity of 35.7% when using the same allergens. This discrepancy could be explained by the limitations of the included studies in

their analysis and the unclear exclusion criteria. In contrast, our study showed that nsIgE had a capacity of over 85% to identify patients with birch-driven, *Alternaria*-driven, and *Phleum*-driven LAR. Nevertheless, these findings were restricted to studies conducted in one or two European institutes, limiting their generalizability.

This meta-analysis is the first to provide pooled clinical utilities of BAT and nEos in diagnosing LAR. Similar to nsIgE, the ability of BAT to identify patients with LAR varied based on the specific allergens tested, with limited generalizability due to the restricted geographical scope of the studies. Additionally, we are the first to highlight significant differences in specificity between nEos and nsIgE or BAT. In contrast, no significant difference in sensitivity was found among the three index tests, as determined through indirect comparisons. These findings were crucial for developing the protocols or guidelines regarding the diagnostic tools for LAR. Lastly, the subgroup analyses and stratifying diagnostic accuracy by allergens revealed the heterogeneity in current evidence, underscoring the need for further research.

Although our study had a strict definition of LAR and encompassed the largest population under its scope, it had several limitations. The major limitation is the heterogeneity of diagnostic accuracy of the index test due to the lack of precise procedural details regarding the timing of nsIgE collection relative to NPT. The presence of dual allergic rhinitis was also not evaluated. Furthermore, the use of different activation markers, such as CD203c instead of CD63, could have led to slight variations in BAT results [40]. Finally, the indirect comparison approach used in our analysis cannot fully substitute for direct comparisons when evaluating the clinical utility of Th2 markers in LAR.

Conclusion

Three Th2-related markers have been investigated for their clinical utility in diagnosing LAR, including nsIgE, BAT, and nEos. Both nsIgE and BAT demonstrated high specificity, supporting their use as confirmatory tests. However, their low sensitivity warrants reconsideration of NPT when results are negative. The heterogeneity observed in pooled data underscores the need for future studies to adopt standardized protocols, thereby minimizing bias and improving the reliability and clinical applicability of these diagnostic tools.

Conflict of interest

Kornkiat Snidvongs has served on the speaker's bureau for Organon and Menarini. All other authors declare no conflicts of interest.

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Authors' contributions

MPH: study design, search, study selection, data collection, data analysis, drafting the article, and final approval. KSe: search, study selection, data collection, revising the article, and final approval. WC: data collection, revising the article, and final approval. KSn: conception, study design, data analysis, drafting the article, and final approval.

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SUPPLEMENTARY MATERIAL

Table S1. Search strategy.

PubMed MEDLINE	EMBASE
#1 "local allergic rhinitis" [All fields] #2 "entopy"[All Fields] #3 "entopic rhinitis" [All Fields] #4 "nonallergic rhinitis" [All Fields] #5 "non-allergic rhinitis" [All Fields] #6 #1 OR #2 OR #3 OR #4 OR #5 #7 "immunoglobulin e"[MeSH Terms] OR "immunoglobulin e"[All Fields] #8 "nasal IgE" [All Fields] #9 "local IgE" [All Fields] #10 "diagnosis"[MeSH Terms] #11 "basophil activation test"[All Fields] #12 "mucosal brush biopsy" [All Fields] #13 "Nasal Cytology" [All Fields] #14 "eosinophilia"[MeSH Terms] OR "eosinophilia"[All Fields] OR "eosinophilias"[All Fields] OR "Nasal eosinophilia"[All Fields] OR "nasal eosinophils" [All Fields] OR "eosinophil count"[All Fields] #15 "nasal specific immunoglobulin E" [All Fields] #16 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 #17 "provocation test" [All Fields] #18 "nasal allergen provocation test" [All Fields] #19 "nose provocation test" [All Fields] #20 "nasal challenge test" [All Fields] #21 "nasal allergen challenge test" [All Fields] #22 "challenge" [All Fields] #23 #17 OR #18 OR #19 OR #20 OR #21 OR #22	1 local allergic rhinitis.mp. 2 entopy.mp. 3 entopic rhinitis.mp. 4 nonallergic rhinitis.mp. 5 1 or 2 or 3 or 4 6 exp immunoglobulin E/ or nasal IgE.mp. 7 local IgE.mp. 8 diagnostic.mp. 9 basophil activation test.mp. or exp basophil activation test/ 10 mucosal brush biopsy.mp. 11 Nasal Cytology.mp. 12 exp eosinophilia/ or Nasal eosinophilia.mp. 13 exp eosinophil count/ or nasal eosinophils.mp. or eosinophil/ 14 nasal specific immunoglobulin E.mp. 15 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 16 exp provocation test/ or nasal allergen provocation test.mp. 17 exp nose provocation test/ or nasal challenge test.mp. 18 nasal allergen challenge test.mp. 19 challenge.mp. 20 16 or 17 or 18 or 19 21 5 and 15 and 20
Web of Science, CENTRAL	
#1 TS= ("local allergic rhinitis" OR "entopy" OR "entopic rhinitis" OR "nonallergic rhinitis") #2 TS= ("immunoglobulin e " OR " nasal IgE *" OR " local IgE " OR " basophil activation test " OR " mucosal brush biopsy " OR "Nasal Cytology" OR "eosinophilia") #3 TS= ("provocation test " OR "nasal allergen provocation test " OR " nose provocation test " OR " nasal challenge test " OR " nasal allergen challenge test ") #4 #1 AND #2 AND #3	

Table S2. Characteristics of nasal allergen provocation test in the included studies.

Study	Allergen concentration	Criteria of positive NPT (Reference test)
Rondon 2007	3	↑ 30% VAS of 5 symptoms AND ↓ 30% in the volume 2-6 cm in AcRh vs. baseline
Rondon 2008	4	↑ 30% VAS of 5 symptoms AND ↓ 30% in the volume 2-6 cm in AcRh vs. baseline
Fuiano 2012	5	Increase TNSS ≥5 points
Gomez 2013	3	↑ 30% VAS of 5 symptoms AND ↓ 30% in the volume 2-6 cm in AcRh vs. baseline
Bozek 2015	1	↑ 30% VAS of 5 symptoms AND ↓ 30% in the volume 2-6 cm in AcRh vs. baseline
Refaat 2015	0	NA
Buntarickpornpan 2016	3	↓ 25% of MCA of the nasal cavity in AcRh vs. baseline OR ↓ 40% of PNIF vs. baseline OR ↓ 20% of PNIF vs. baseline AND Lebel score ≥5
Krajewska-Wojtys 2016	1	↑ 30% VAS of 5 symptoms AND ↓ 30% in the volume 2-6 cm in AcRh vs. baseline
Zicari 2016	1	↑ 50% unilateral nasal resistance at 150 Pa in AAR vs. baseline
Krajewska-Wojtys 2017	1	↑ 30% VAS of 5 symptoms AND ↓ 30% in the volume 2-6 cm in AcRh vs. baseline
Tao 2018	1	↑ 30% VAS of 5 symptoms AND ↑100% total nasal resistance at 150 Pa vs. baseline or ↑15% in eosinophil ratio in the nasal secretion smear
Duarte Ferreira 2019	3	↑ 30% VAS of 5 symptoms AND/ OR ↑ 50% unilateral nasal resistance at 150 Pa in AAR vs. baseline
Meng 2019	4	Total symptom score was ≥4 OR ↓ 60% in nasal air flow in AAR vs. baseline OR ↓ 20% in nasal air flow plus total symptom score was ≥3
Phothijindakul 2019	2	≥3 of total VAS AND ↓ 30% in the volume of MCA in AcRh vs. baseline
Bozek 2020	1	↑ 30% VAS of 5 symptoms AND ↓ 30% in the volume 2-6 cm in AcRh vs. baseline
Eckrich 2020	1	↓ 40% of PNIF vs. baseline OR Lebel score ≥6
Santamaria 2020	1	↓ 20% in the volume 2-6 cm in AcRh vs. baseline OR ↑ 3 points of Lebel score OR ↑ 30% VAS of 5 symptoms
Tantilipikorn 2021	3	↓ 25% of MCA of the nasal cavity in AcRh vs. baseline OR ↓ 40% of PNIF vs. baseline OR ↓ 20% of PNIF vs. baseline AND Lebel score ≥5
Testera-Montes 2021	1	↑ 30% VAS of 5 symptoms AND ↓ 30% in the volume 2-6 cm in AcRh vs. baseline
Gonzalez-Torres 2023	3	↑ 23% VAS of 5 symptoms
Testera-Montes 2024	1	↓ 40% in the volume 2-6 cm in AcRh vs. baseline OR ↑ 5 points of Lebel score OR ↓ 30% in the volume 2-6 cm in AcRh vs. baseline AND ↑ 3 points of Lebel score

Abbreviations: NPT, nasal allergen provocation test; VAS, visual analogue scale; TNSS, total nasal symptom score; AcRh, acoustic rhinometry; AAR, active anterior rhinomanometry; PNIF, peak nasal inspiratory flow.

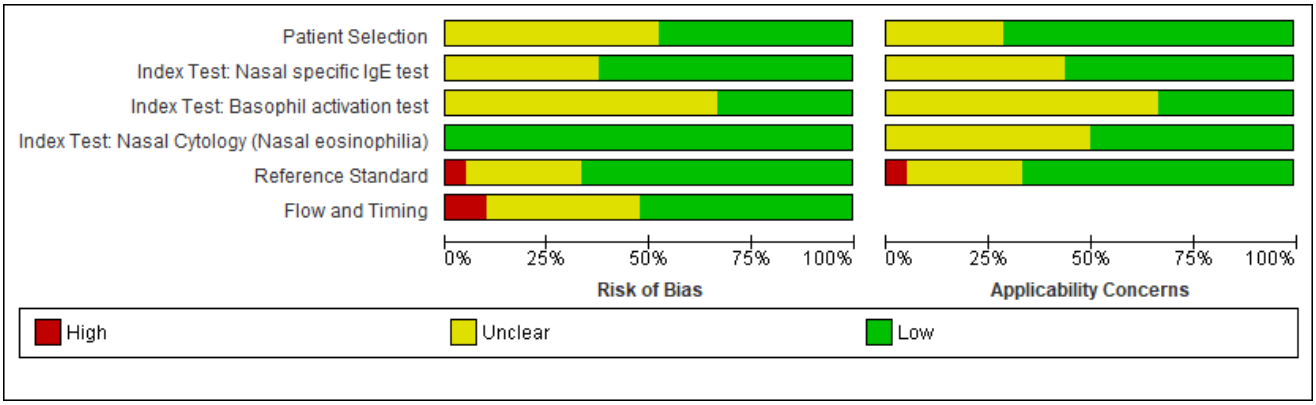

Figure S1. Risk of bias and applicability concerns graph.

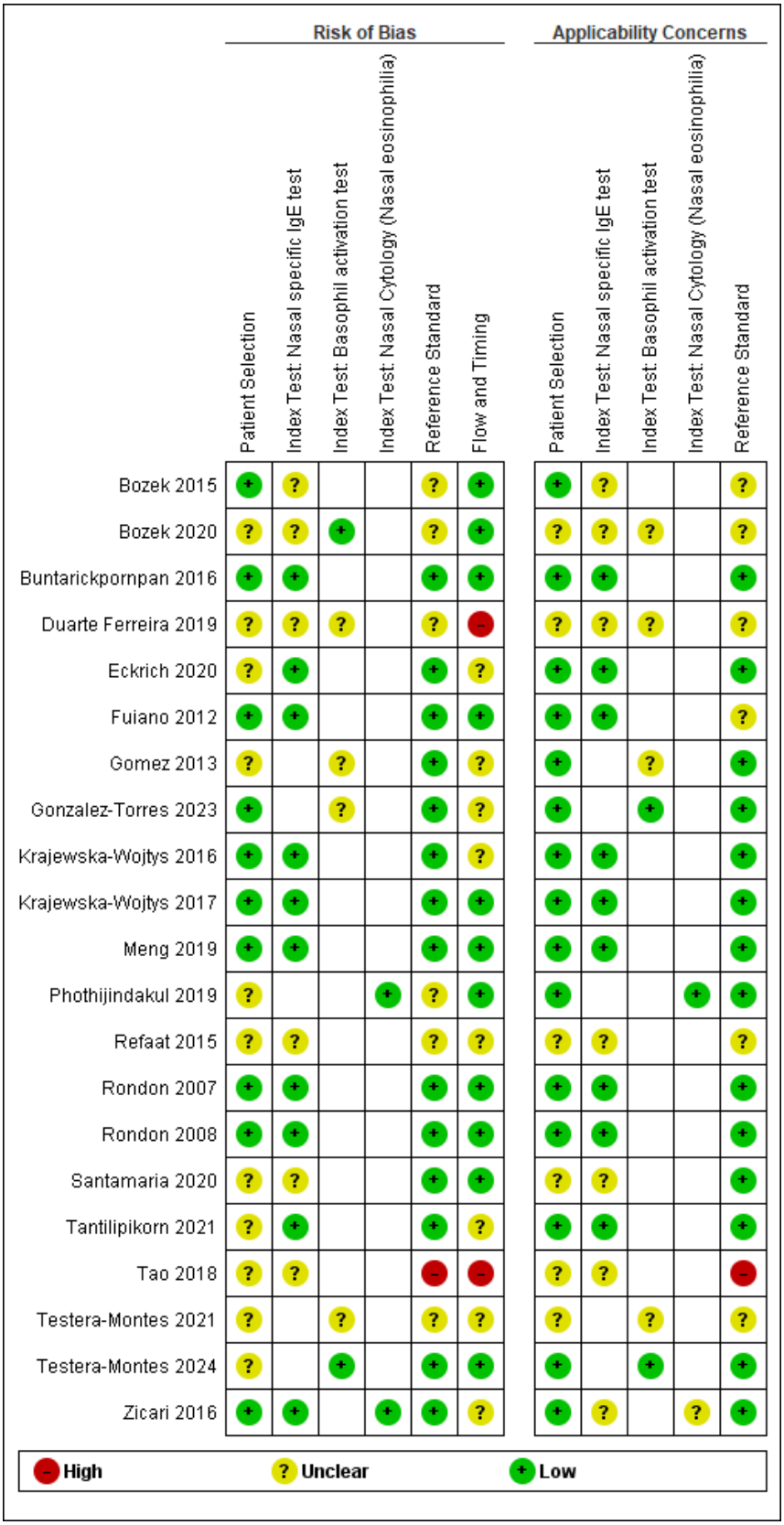

Figure S2. Risk of bias and applicability concerns summary.

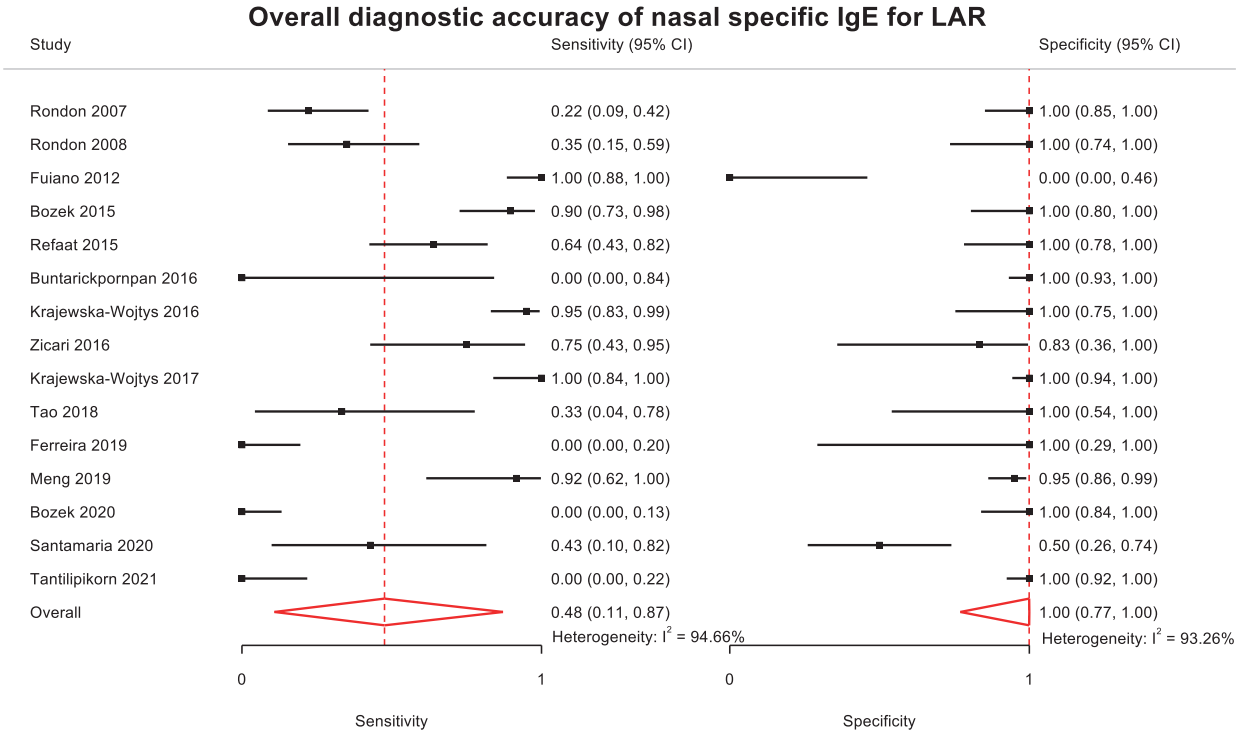

Figure S3. Overall diagnostic accuracy of nasal specific IgE for local allergic rhinitis.

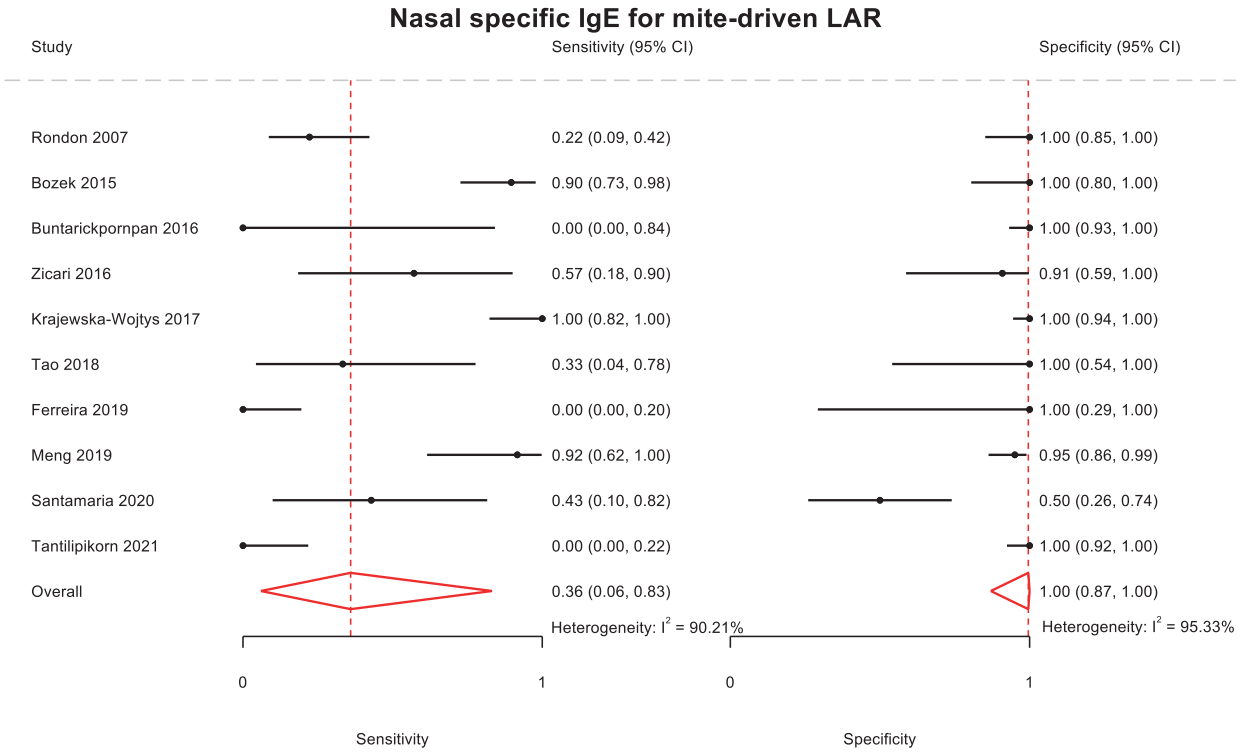

Figure S4. Diagnostic accuracy of nasal specific IgE for mite-driven local allergic rhinitis.

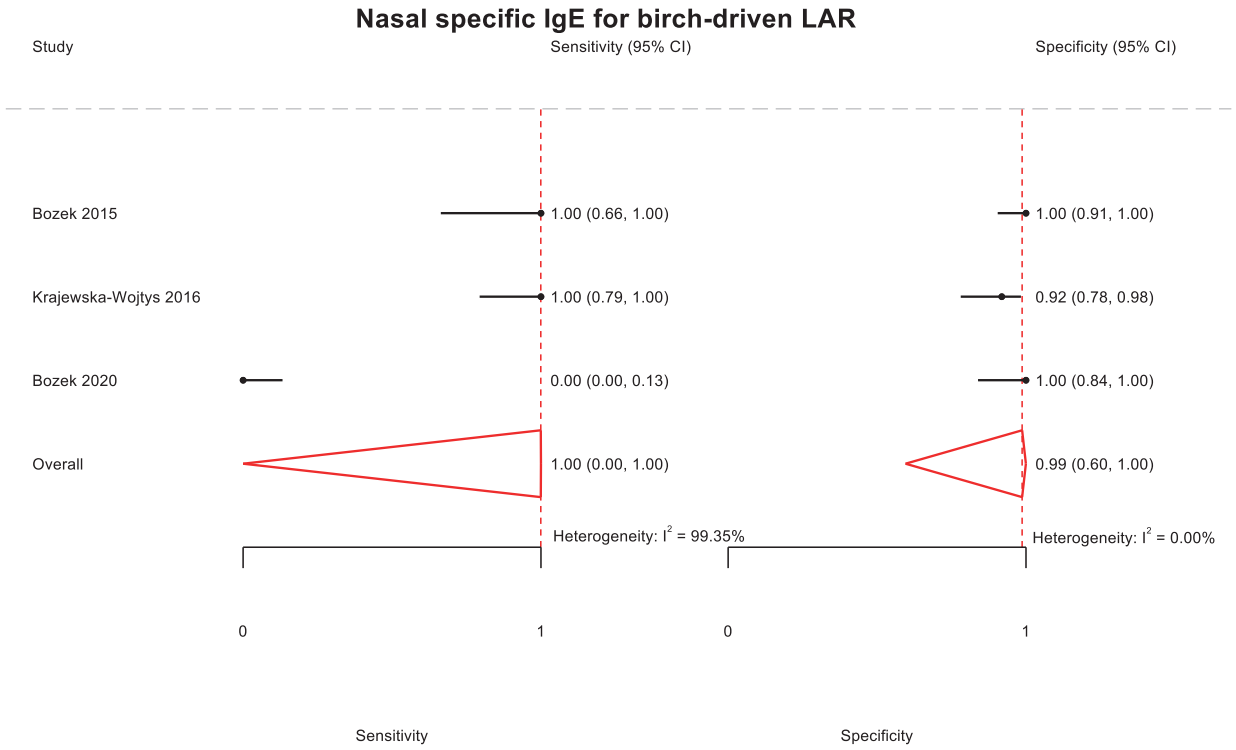

Figure S5. Diagnostic accuracy of nasal specific IgE for birch-driven local allergic rhinitis.

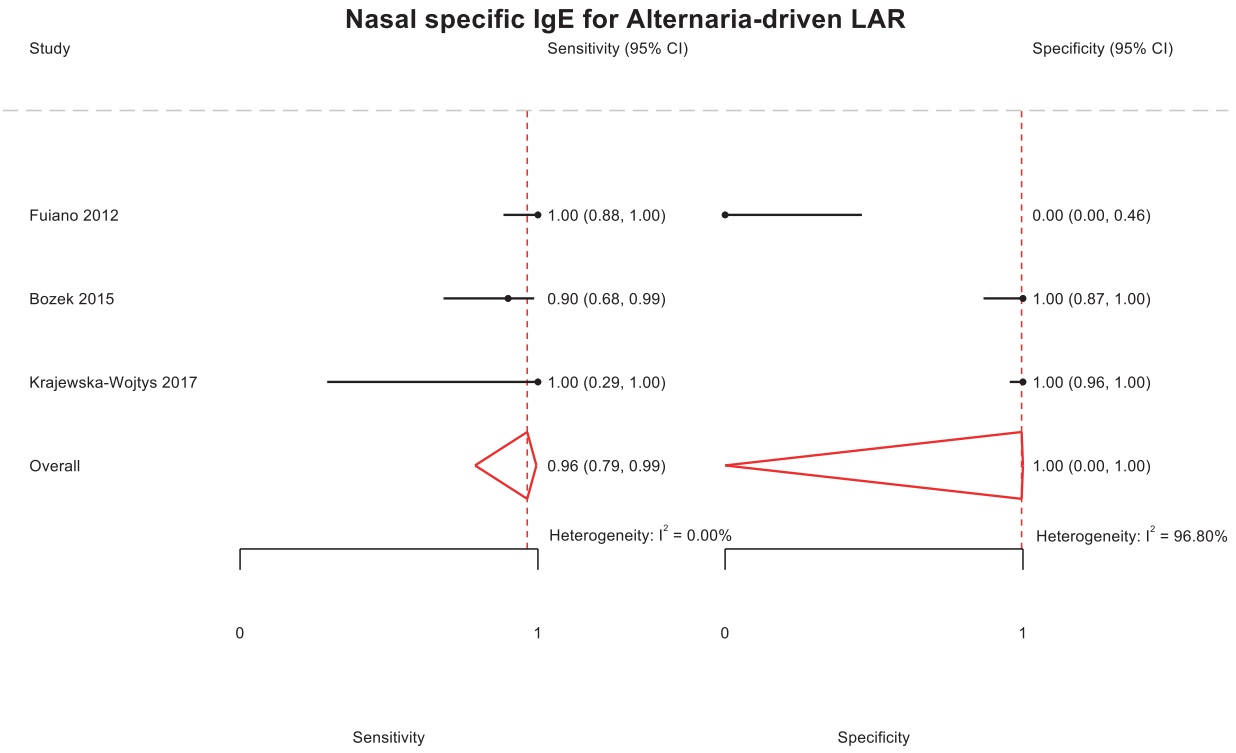

Figure S6. Diagnostic accuracy of nasal specific IgE for Alternaria-driven local allergic rhinitis.

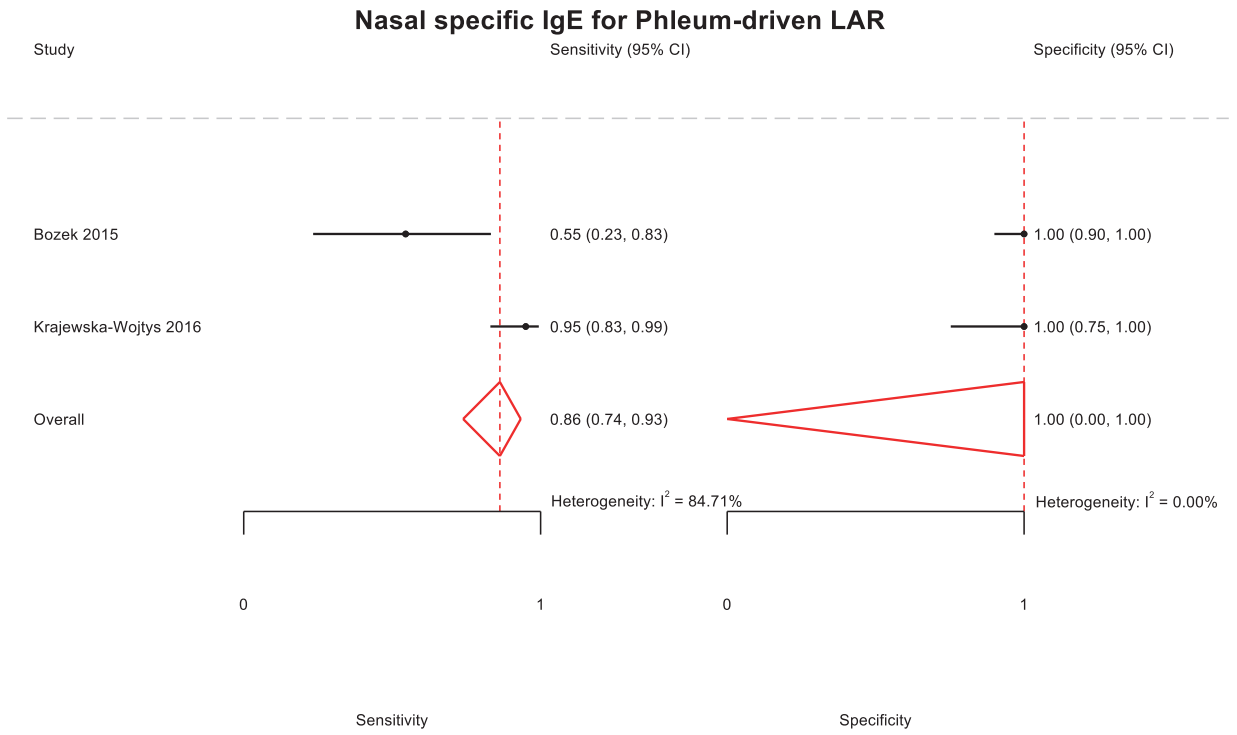

Figure S7. Diagnostic accuracy of nasal specific IgE for Phleum-driven local allergic rhinitis.

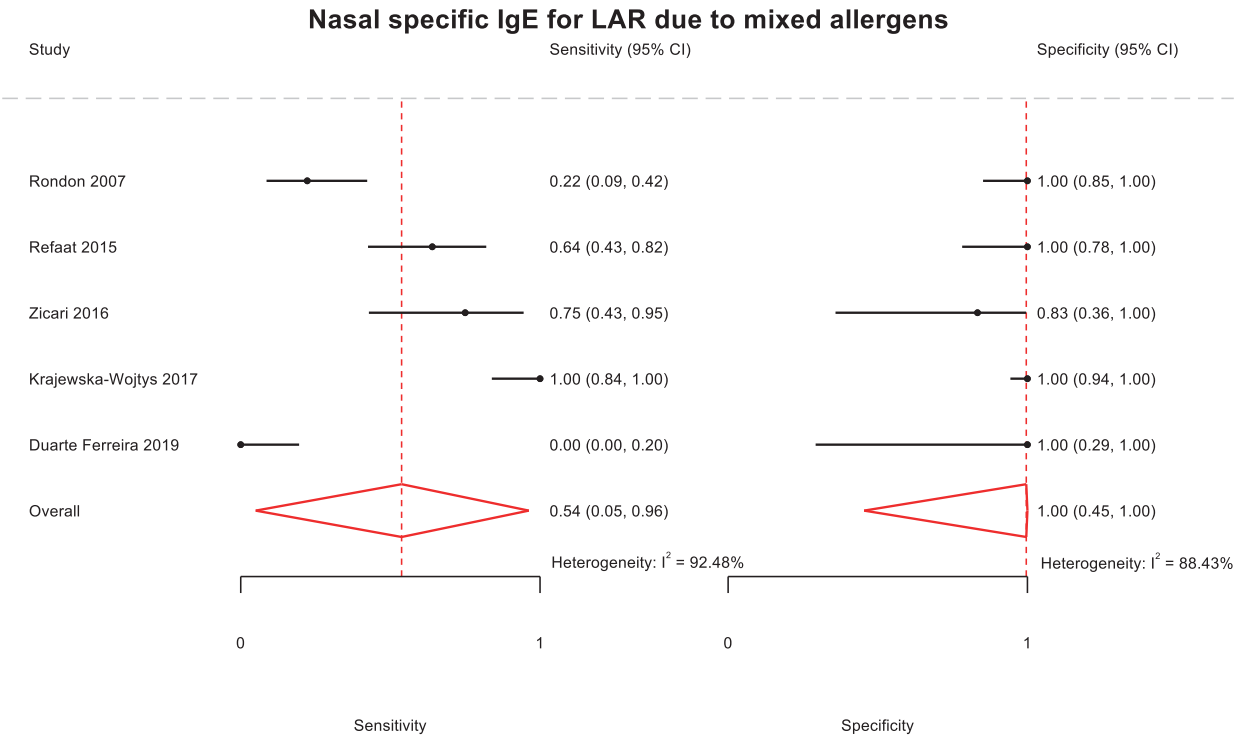

Figure S8. Diagnostic accuracy of nasal specific IgE for local allergic rhinitis due to mixed allergens.

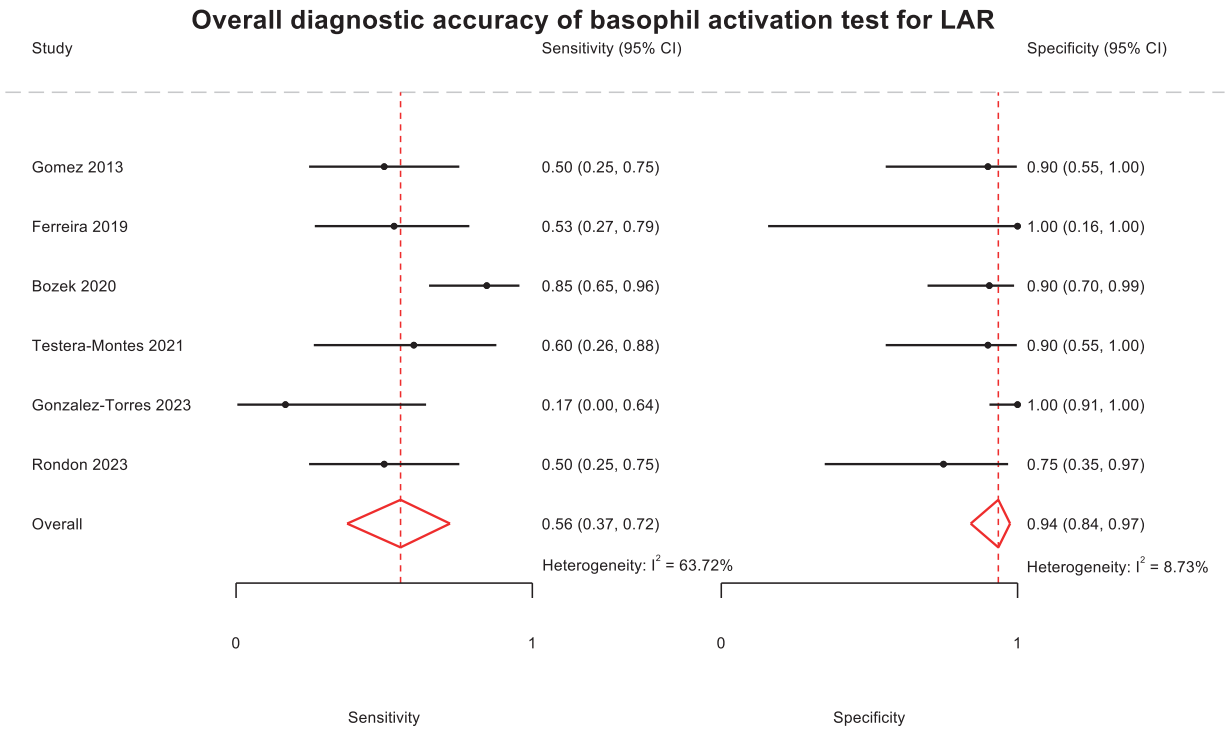

Figure S9. Overall diagnostic accuracy of basophil activation test for local allergic rhinitis.

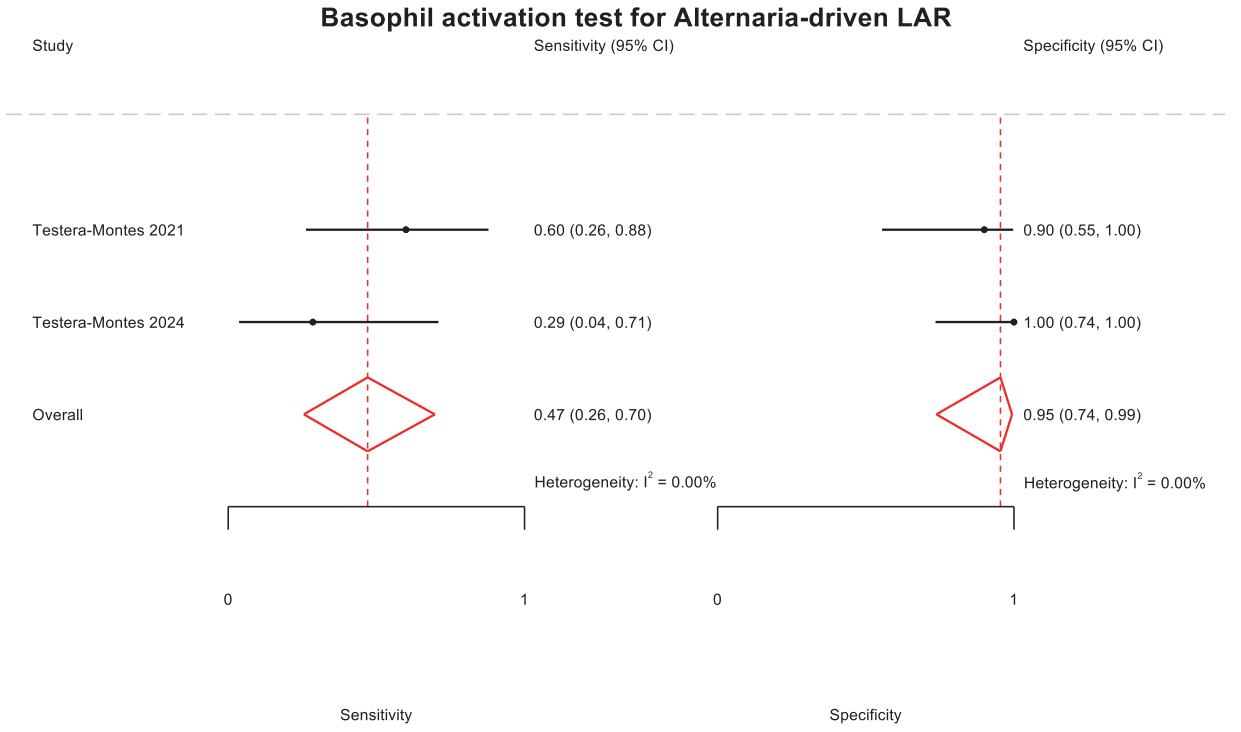

Figure S10. Diagnostic accuracy of basophil activation test for mite-driven local allergic rhinitis.

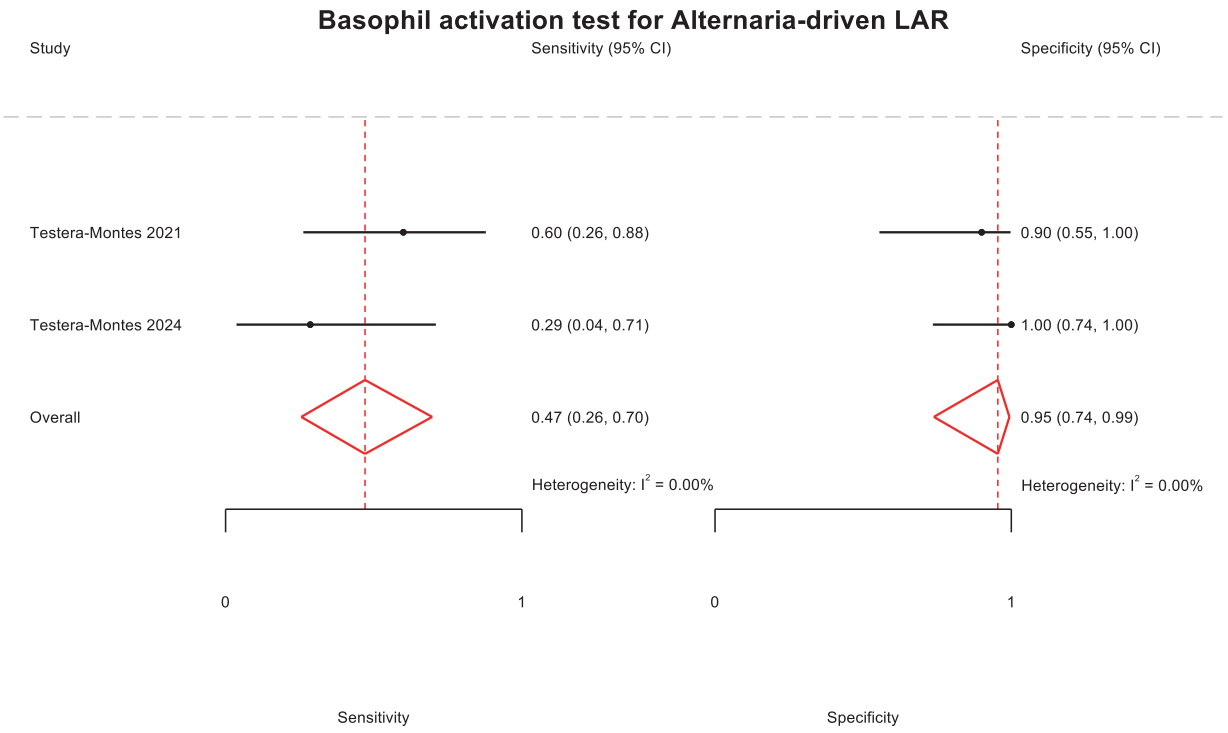

Figure S11. Diagnostic accuracy of basophil activation test for Alternaria-driven local allergic rhinitis.

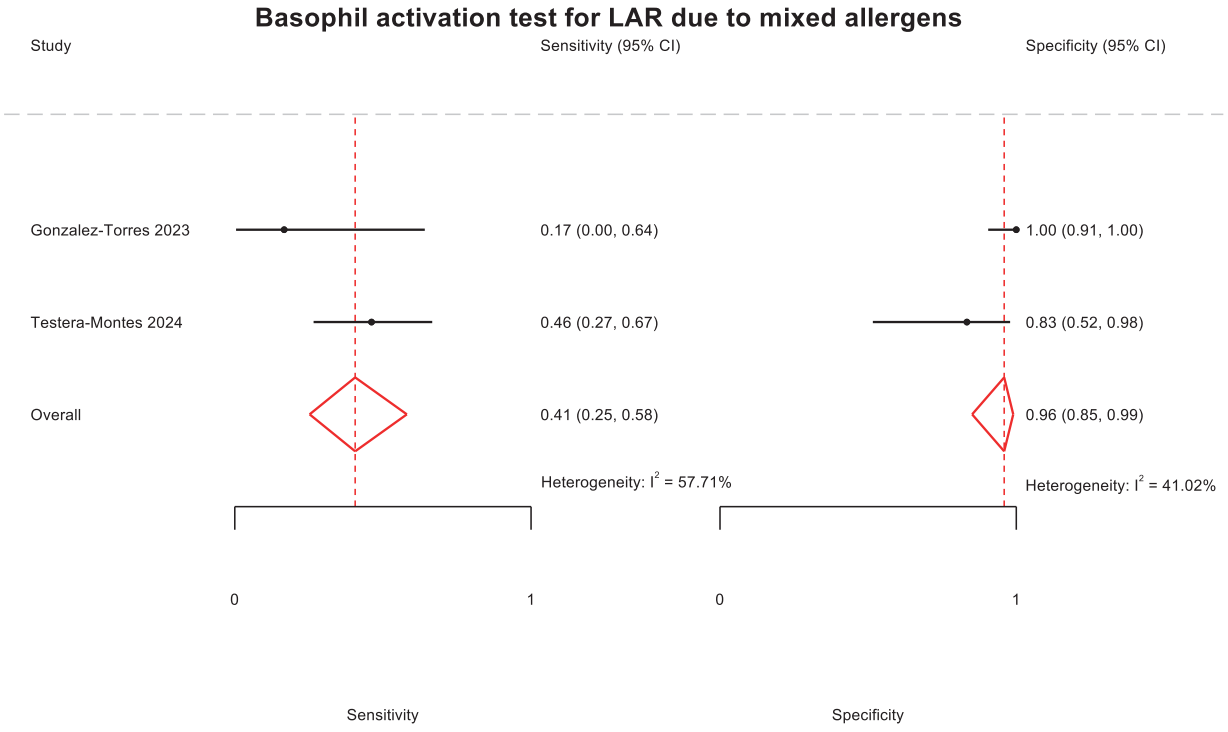

Figure S12. Diagnostic accuracy of basophil activation test for local allergic rhinitis due to mixed allergens.

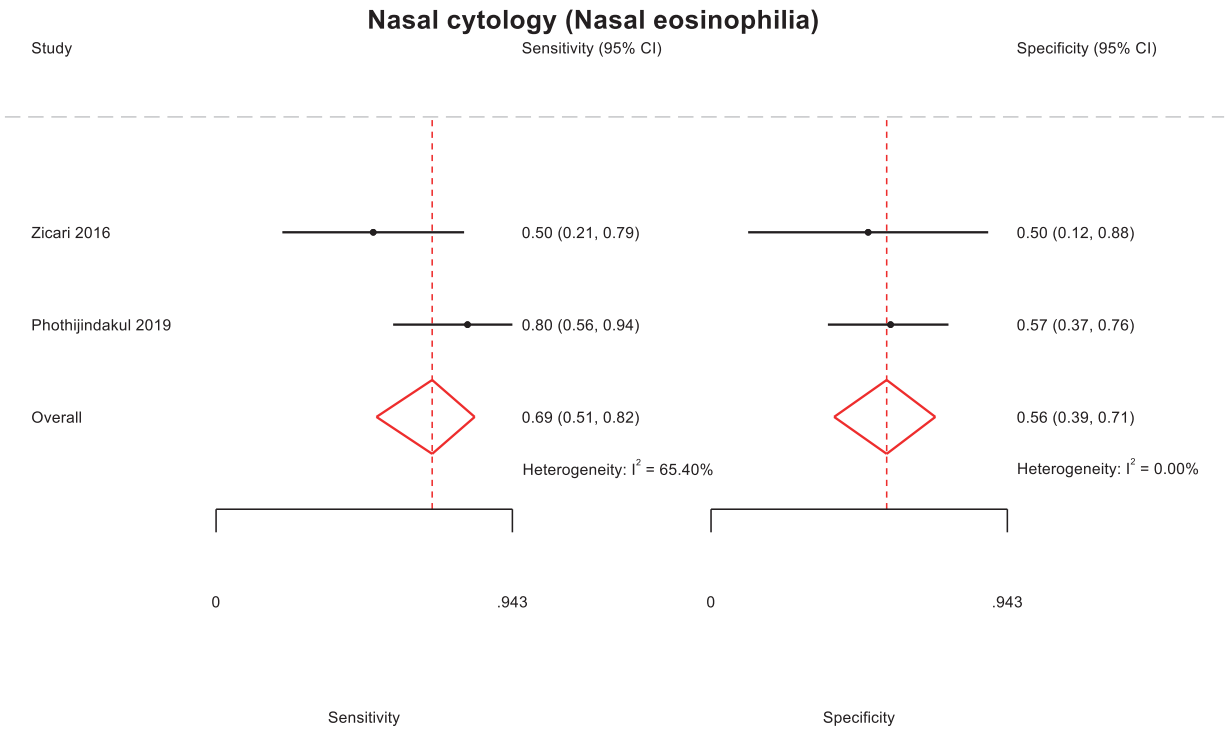

Figure S13. Accuracy of nasal cytology with nasal eosinophilia condition in detecting local allergic rhinitis.

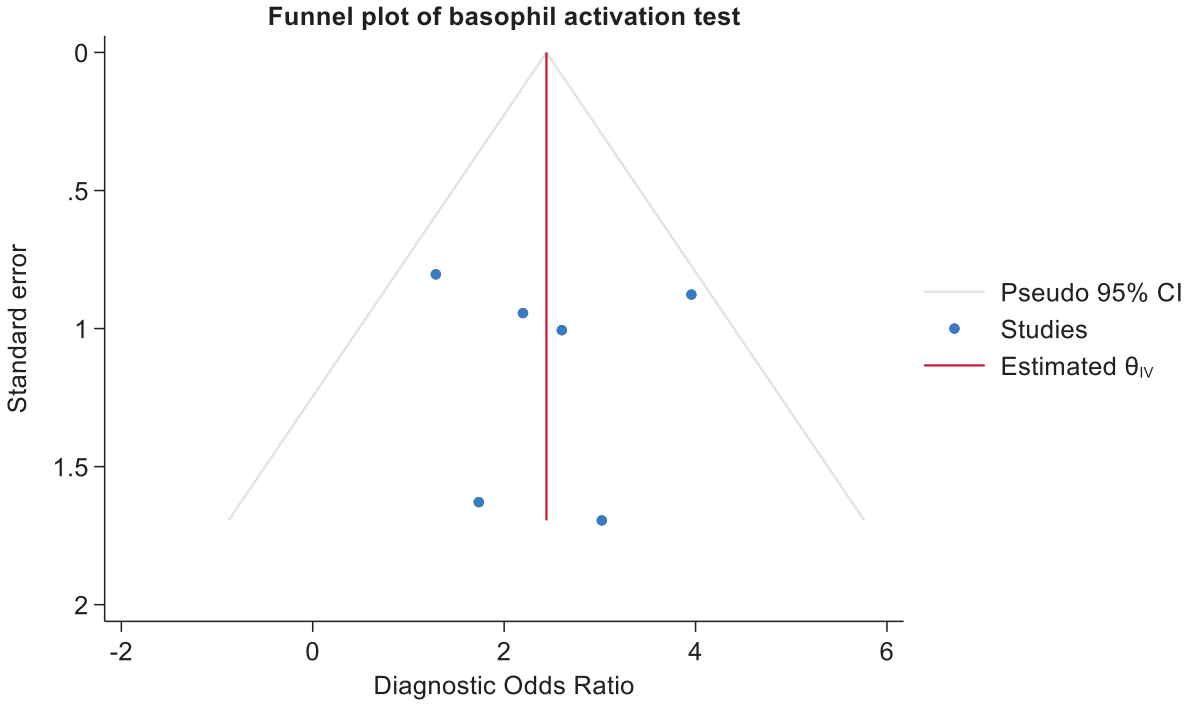

Figure S14. Funnel plots of diagnostic odds ratio of nasal specific IgE.

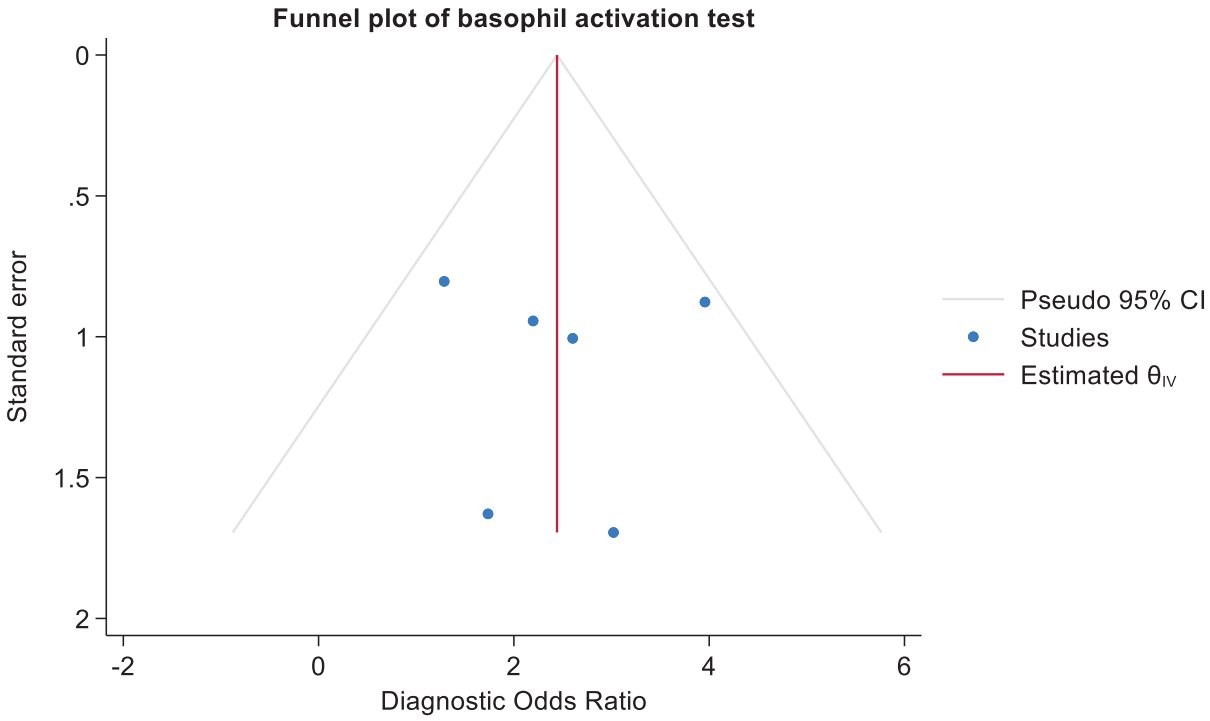

Figure S15. Funnel plots of diagnostic odds ratio of basophil activation test.

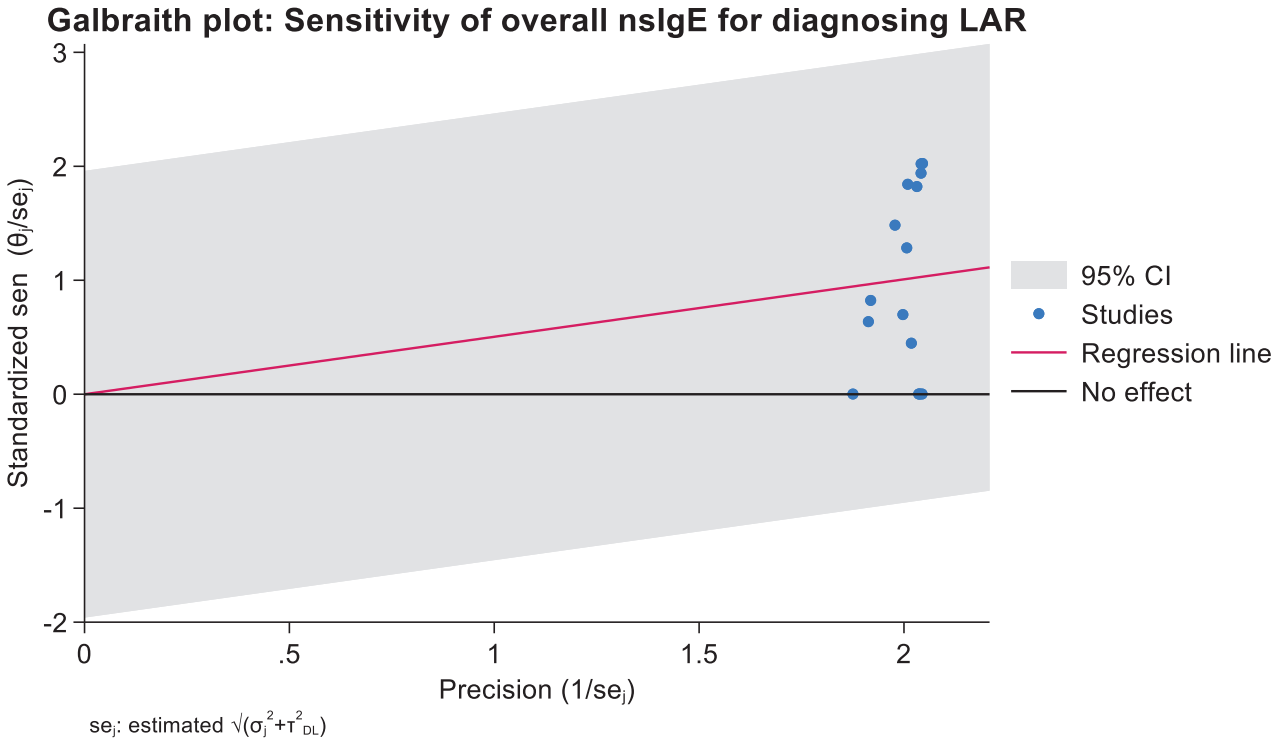

Figure S16. Galbraith plot of the sensitivity of overall nsIgE for diagnosing local allergic rhinitis.

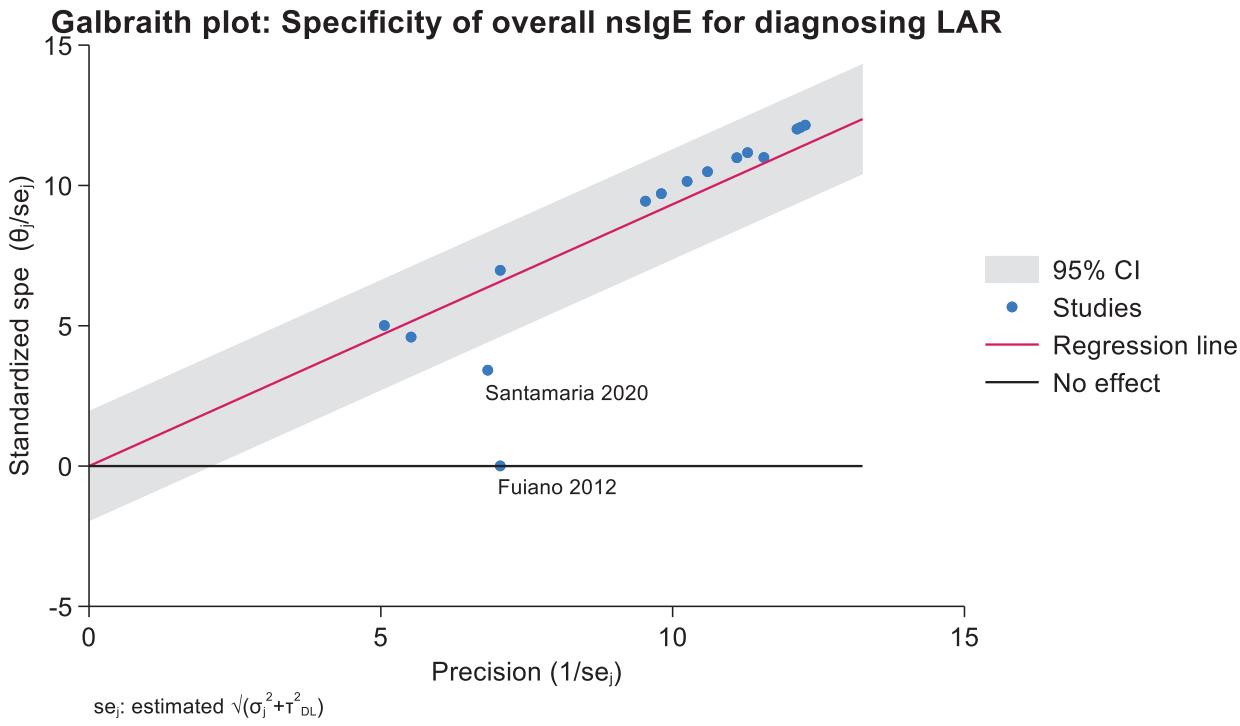

Figure S17. Galbraith plot of the specificity of overall nsIgE for diagnosing local allergic rhinitis.

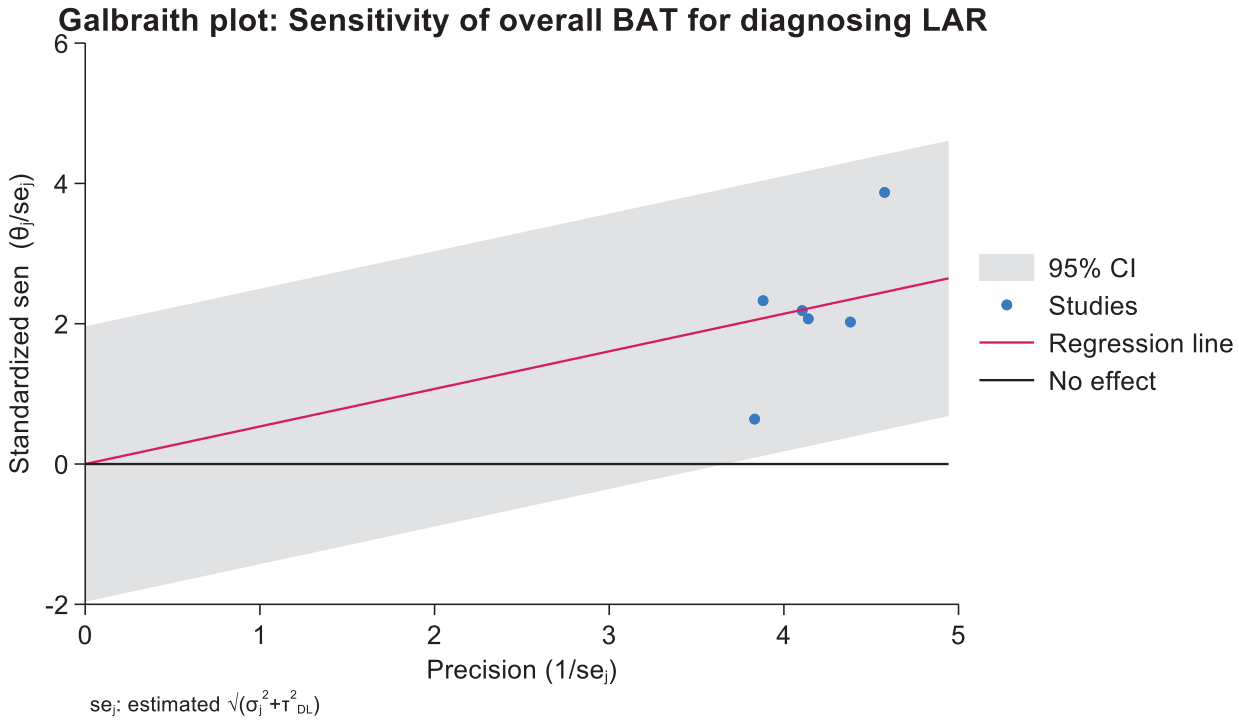

Figure S18. Galbraith plot of the sensitivity of overall BAT for diagnosing local allergic rhinitis.

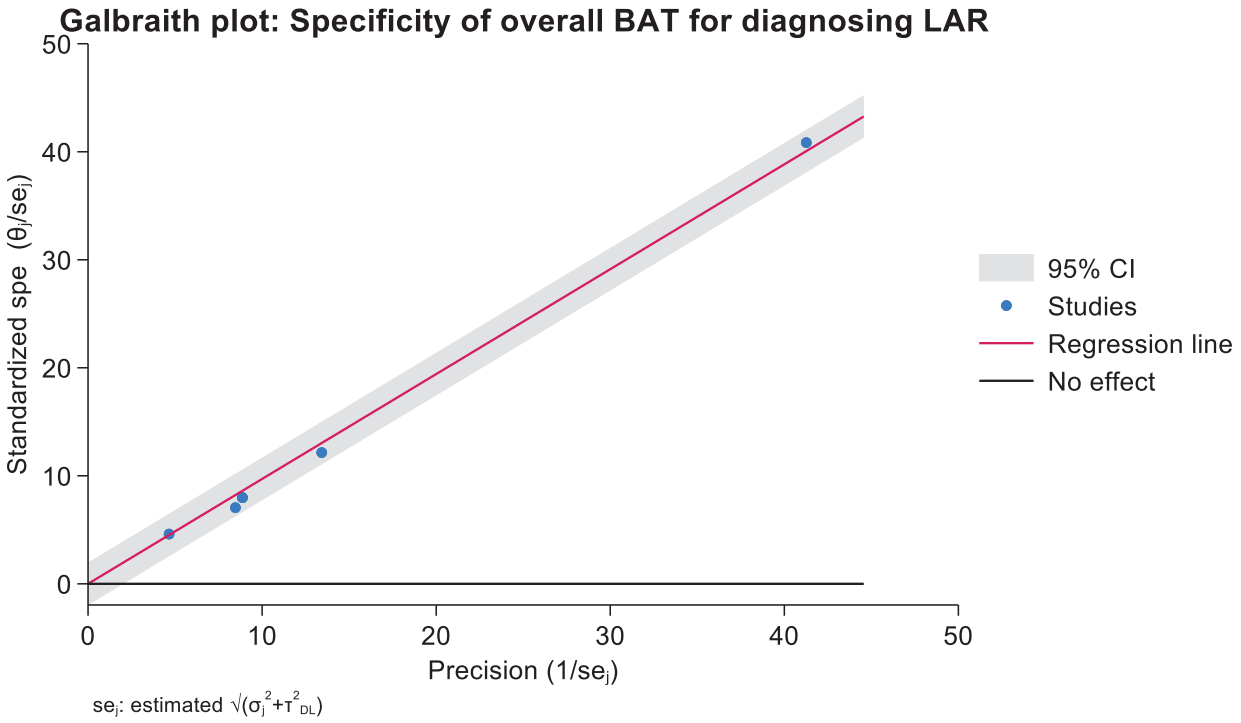

Figure S19. Galbraith plot of the specificity of overall BAT for diagnosing local allergic rhinitis.

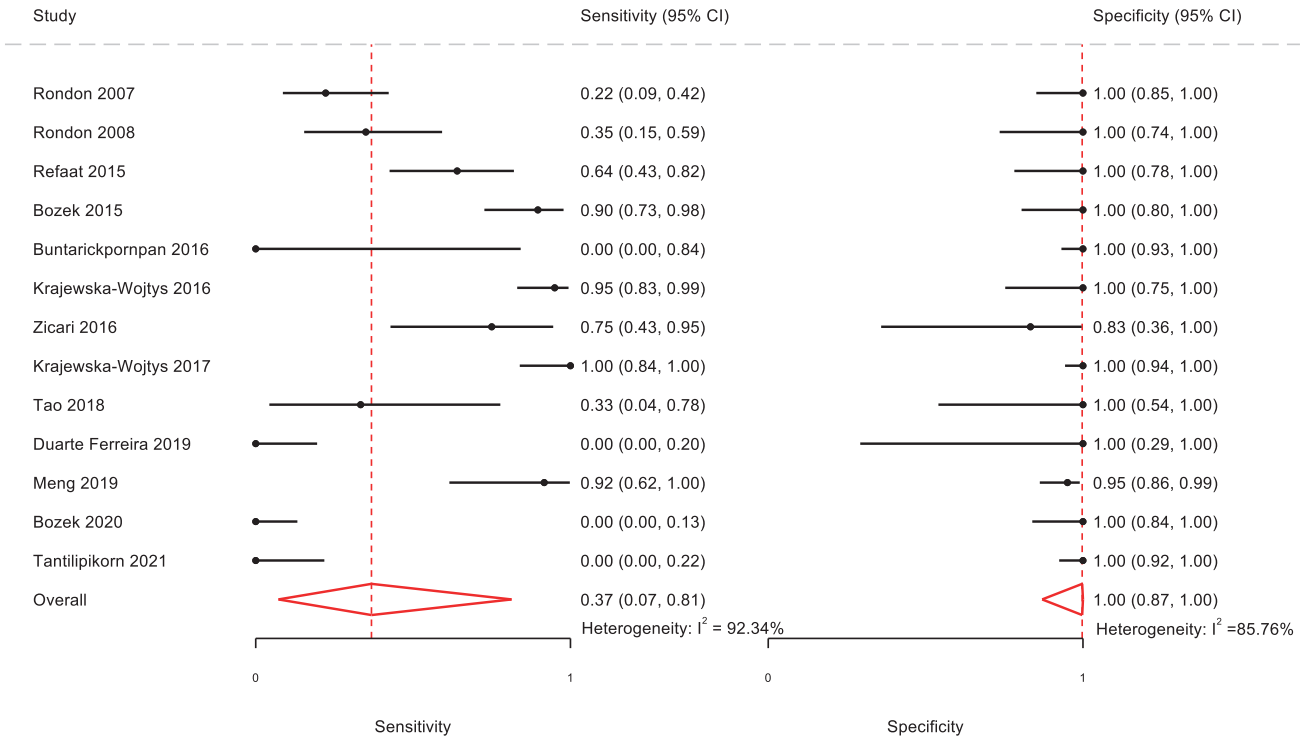

Figure S20. Sensitivity analysis of diagnostic accuracy of overall nasal specific IgE for local allergic rhinitis by removing 2 studies with the potential source of heterogeneity

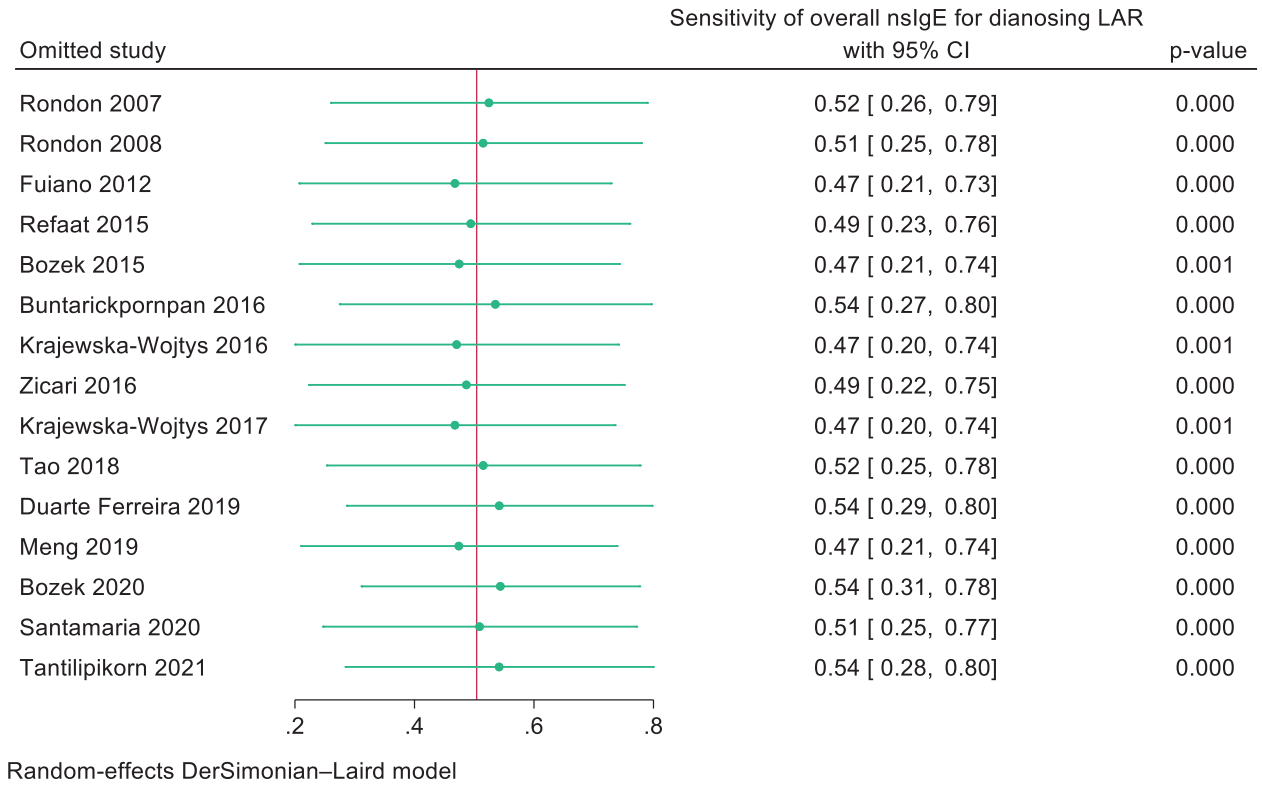

Figure S21. Sensitivity analysis for the sensitivity of overall nsIgE for diagnosing local allergic rhinitis by leave-one-out method.

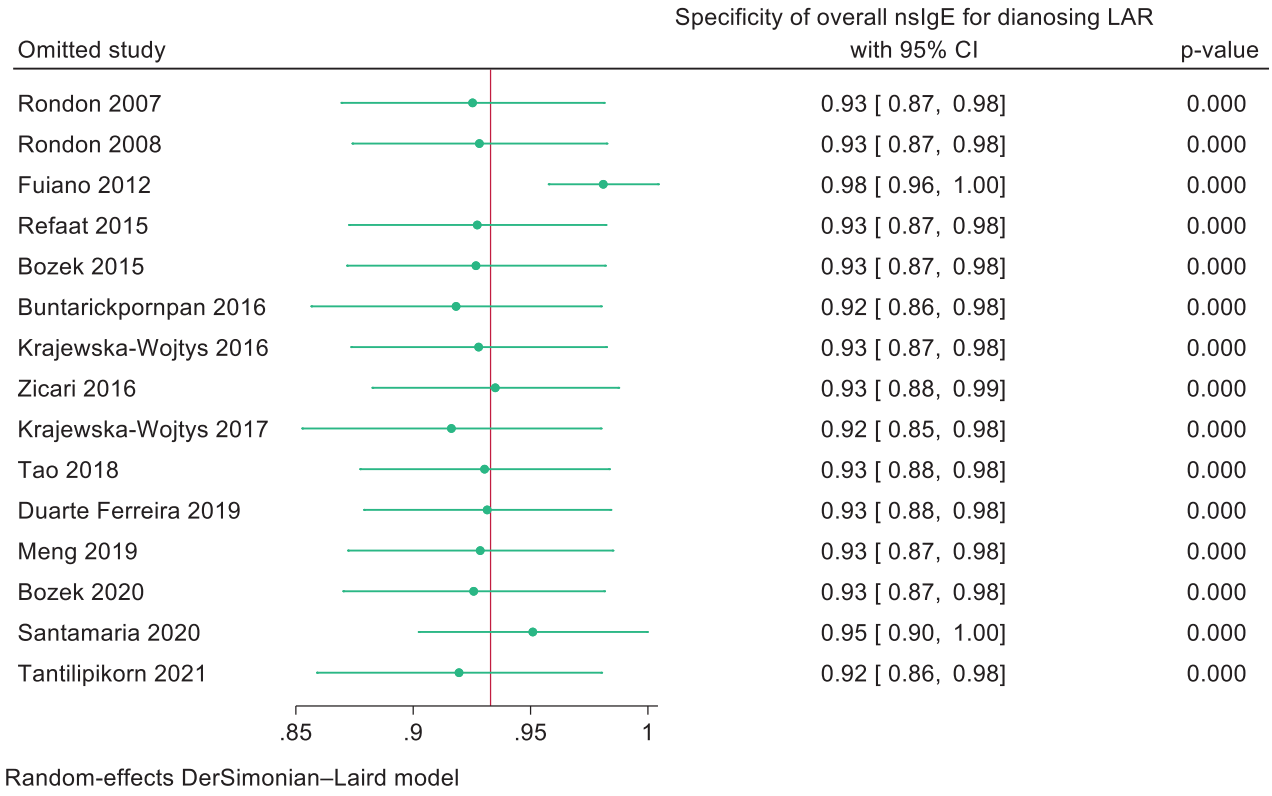

Figure S22. Sensitivity analysis for the specificity of overall nsIgE for diagnosing local allergic rhinitis by leave-one-out method.

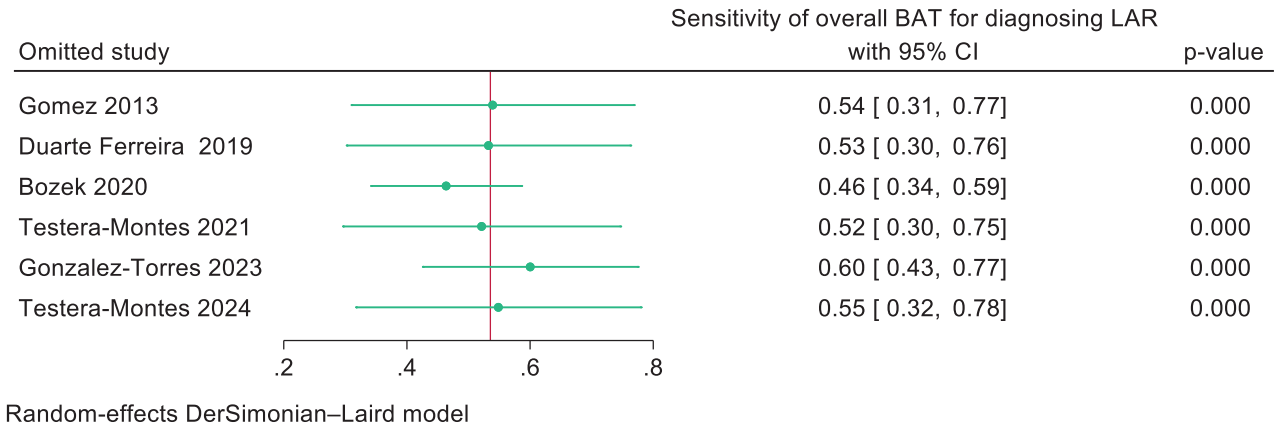

Figure S23. Sensitivity analysis for the sensitivity of overall BAT for diagnosing local allergic rhinitis by leave-one-out method.

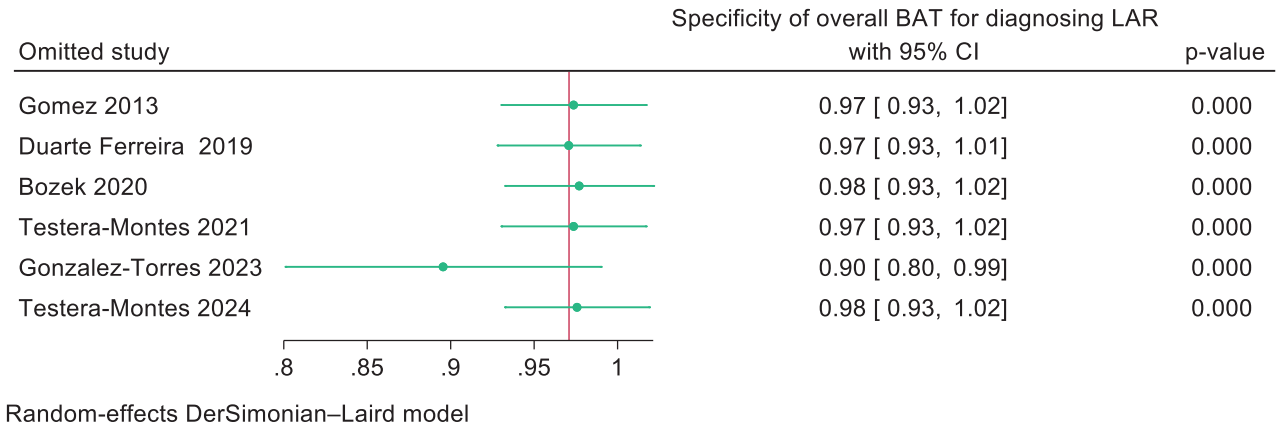

Figure S24. Sensitivity analysis for the specificity of overall BAT for diagnosing local allergic rhinitis by leave-one-out method.