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Review

Diagnostic value of Der p 1 and Der p 2 specific IgE in *Dermatophagoides pteronyssinus* IgE sensitization

Xin Yang, MS [*,†,‡]; Gaowei Fan, MS [*,†]; Jinming Li, PhD [*,†]

[*] National Center for Clinical Laboratories, Beijing Hospital, Beijing, People's Republic of China
[†] Graduate School, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, People's Republic of China
[‡] Yantai Yuhuangding Hospital, Yantai, Shandong Province, People's Republic of China

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ABSTRACT

Objective: To assess the diagnostic performance of Der p 1 and Der p 2 specific IgE (sIgE).
Data Sources: Studies were systematic computerized searches of the PubMed, EMBASE, and Cochrane libraries (published 1966 to September 5, 2015).
Study Selection: Records were screened by title and abstract and then by full-text articles of relevant studies. Eligible studies were selected according to inclusion criteria: (1) all house dust mite allergy diagnosed on the basis of clinical symptoms in combination with a dust mite extract skin prick test result; (2) the inclusion of controls in the study; and (3) enough data to construct the diagnostic 2 × 2 table. True-positive, false-positive, false-negative, and true-negative values were extracted from or calculated for each study. Then the pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio were calculated. A summary receiver operating characteristic curve and area under the curve were used to evaluate the overall diagnostic performance.
Results: Seven eligible studies that involved 1040 cases were included in this meta-analysis. The meta-analysis found that detection of Der p 1 or Der p 2 sIgE is of sufficient diagnostic accuracy for use in the diagnosis of Dermatophagoides pteronyssinus IgE sensitization.
Conclusion: Detection of Der p 1 or Der p 2 sIgE is a promising diagnostic tool in the diagnosis of *D pteronyssinus* IgE sensitization.
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Introduction

House dust mites (HDMs) are among the most important allergen sources in the world.[1,2] Although many different species of HDM have been reported to occur in indoor environments, *Dermatophagoides pteronyssinus* and *Dermatophagoides farina* are the primary species associated with the development of *D pteronyssinus* IgE sensitization.[3] To date, 23 different *D pteronyssinus* allergens have been characterized, but many studies have found that group 1 (Der p 1) and group 2 (Der p 2) allergens represent the *D pteronyssinus* allergens with the greatest clinical significance.[4]

So far, in the diagnosis of *D pteronyssinus* IgE sensitization, the use of a skin prick test (SPT) using crude extract has been considered standard when considered in combination with case history.[5] However, this method has many disadvantages. For instance, there are many conditions under which SPTs cannot be performed, including diffuse skin disease, significant dermatographism, inability to wean off medications that may interfere with testing, or the use of an extract believed to have a high probability of inducing a systemic reaction in the individuals.[6] In addition, mite extracts contain a number of well-characterized allergens, and mite-sensitized patients could experience differential levels of IgE reactivity toward them. Furthermore, standardized testing is difficult to implement because of variations that exist in the quality and/or potency of commercially available extracts caused by the complexity of the components used in SPTs.[7]

The clinical utility of measuring the levels of IgE against natural Der p 1 and recombinant Der p 2 has been validated as a diagnostic tool for *D pteronyssinus* IgE sensitization detection,[5] but because of inconsistent results among studies,[8–14] it has not been possible to draw firm conclusions. Evaluating sensitization to Der p 1 and Der p 2 is also considered an important step in the selection of patients suitable for allergen immunotherapy using HDM extract.[15] As evidence accumulates, many results raise concerns about the diagnostic value of Der p 1 and Der p 2 specific IgE (sIgE). To address this issue, we performed this meta-analysis to evaluate the diagnostic performance of serum Der p 1 and Der p 2 sIgE in the detection of *D pteronyssinus* IgE sensitization.

Reprints: Jinming Li, PhD, National Center for Clinical Laboratories, Beijing Hospital, No. 1 Dahua Rd, Dongdan, Beijing 100730, People's Republic of China; E-mail: jmli@nccl.org.cn.
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Methods and Results

Literature Search

We performed systematic computerized searches of the PubMed, EMBASE, and Cochrane libraries to identify relevant studies (published 1966 to September 5, 2015) using combinations of the following search terms: *Der p 1* OR *Der p 2* AND *IgE* OR *immunoglobulin E* AND *(house dust mite)* OR *Pyroglyphidae* OR (Dermatophagoides pteronyssinus) OR *HDM* AND *allergy* OR *hypersensitivity*. Our literature search was limited to published studies that focused on human beings and were written in English. In addition, a manual search was performed using references from relevant literature to identify additional eligible studies. Articles were excluded if they were review articles or unrelated studies (not relevant to our research). When multiple publications about a single study were identified, only those representing the latest reference and reporting the outcomes were included. We had already contacted the corresponding authors by email for those unpublished data of some literatures but did not get responses from them; therefore, their studies were excluded. In addition, we also manually screened the studies listed in the references of included studies.

Inclusion and Exclusion Criteria

Records retrieved from databases and reference lists were first screened by title and abstract, after which full-text articles of relevant studies were retrieved for further review. Eligible studies were selected according to the following inclusion criteria: (1) all HDM allergy diagnosed on the basis of clinical symptoms in combination with a dust mite extract SPT; (2) the inclusion of controls in the study; and (3) enough data to construct the diagnostic 2×2 table. All records were independently reviewed by 2 authors (X.Y. and G.F.), who reached a consensus about each eligible study.

Data Extraction

The following data were extracted by the 2 authors independently (X.Y. and G.F): name of author, year of publication, country where the study was conducted, number of study participants, ages of study participants, methods for Der p sIgE detection, and true-positive (TP), false-positive (FP), false-negative (FN), and true-negative (TN) results. When multiple methods were used for Der p sIgE detection in the sera, the methods with the greatest sensitivity or specificity were extracted. To explore the heterogeneity, the analyses were stratified by center within study (published time and sample size). According to the sample size, eligible studies were classified as large (>100 participants) or small (≤100 participants); according to the published time, these studies were classified as 2 subgroups (before 2011, 2011 or later). A third author (J.L.) assessed the data and resolved any disagreements.

Quality Assessment

Methodologic quality of eligible studies was evaluated by 2 investigators (X.Y. and G.F.) using the improved QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) tool.[16] QUADAS-2 is designed to evaluate the quality of primary diagnostic accuracy studies, which consists of 4 crucial domains (patient selection, index test, reference standard, and flow and timing). With signaling questions, the risk of bias and concerns regarding applicability (with the exception of the flow and timing domain) were judged as low, high, or unclear. A summary of the QUADAS plot was generated using the Review Manager software program, version 5.3 (Cochrane Collaboration).

Statistical Analysis

The pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), positive predicted value, negative predicted value, diagnostic odds ratio (DOR), and corresponding 95% confidence intervals (CIs) were calculated using the accuracy data (TP, FP, FN, and TN) extracted from each eligible study. The PLR was calculated as sensitivity/(1 − specificity), and the NLR was calculated as (1 − sensitivity)/specificity. A clinically useful test was defined with a PLR greater than 5.0 and an NLR less than 0.2. DOR is a measure that combined sensitivity and specificity and is defined as PLR/NL.[17] In addition, the summary receiver operating characteristic (SROC) curve was generated and the area under the curve (AUC) was calculated.

The Spearman correlation between the logit of sensitivity and the logit of 1 − specificity was calculated to determine the threshold effect, with $P < .05$ considered indicative of a significant threshold effect. The heterogeneity caused by a nonthreshold effect was measured using a Q test and the inconsistency index (I^2), with $P \leq .05$ and an I^2 of 50% or higher considered indicative of significant heterogeneity caused by a nonthreshold effect. In the presence of significant heterogeneity, subgroup analyses were performed for sample size and publication year to detect the source. Publication bias was detected using the Deek's funnel plot,[18] and $P < .05$ was considered indicative of the presence of publication bias. All statistical analyses were performed using STATA software, version 12.0 (StataCorp, College Station, Texas) with the MIDAS module and Meta-DiSc.

Study Selection

As shown in Figure 1, after duplicates, reviews, and unrelated articles were removed, 41 full-text articles were selected for further evaluation of eligibility.[3,5,8–15,19–49] After rigorous evaluation, 7 eligible studies were identified and included in the meta-analysis.[8–14] The main reasons for exclusion were no control subjects (n = 19),[3,5,15,19–34] no SPT performed (n =11),[35–45] and insufficient data to construct 2×2 tables (n = 4).[46–49] No additional studies were identified by searching the references of eligible studies or relevant reviews.

Characteristics of Eligible Studies

The baseline characteristics of the eligible studies are listed in Table 1. All eligible studies were published between 1988 and 2012. The QUADAS-2 summary plot is presented in Figure 2. As shown,

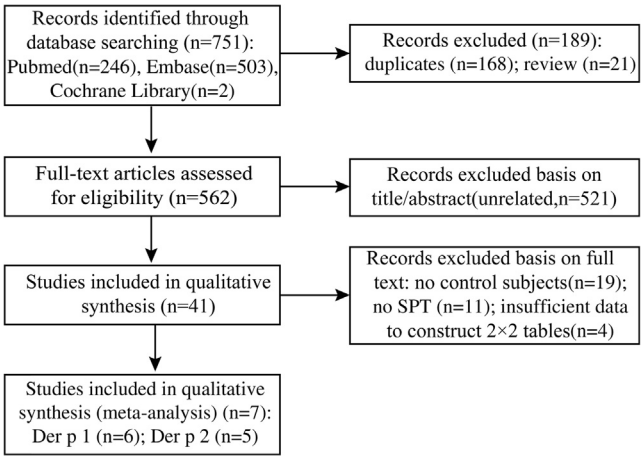

Figure 1. Flow diagram of study selection. SPT indicates skin prick test.

Table 1
Characteristics of Eligible Studies

Source	Year	Country	Total (A/C)	Age, y	SPT Ingredient	Diagnostic Standard Wheal Size, mm	Index Test	Method	Threshold
Miranda et al[13]	2011	Japan	86 (72/14)	Range, 5–15	*Dermatophagoides pteronyssinus, Dermatophagoides farinae, Blomia tropicalis*	≥3	Der p sIgE	rELISA	EI >1.2
Stewart et al[11]	1988	Australia	51 (42/9)	…[a]	*D pteronyssinus* and histamine	≥2	Der p sIgE	RAST	3% Radiation bound
Taketomi et al[10]	2006	United States	77 (47/30)	Mean (range), 43 (18–60)	*D pteronyssinus*	>3	Der p sIgE	rELISA	5 EU/mL
Araujo et al[14]	2012	Italy	101 (89/12)	Range, 6–15	*D pteronyssinus, Blattella germanica*, cat and dog	≥2	Der p sIgE	ImmunoCAP	0.3 ISU
Silva et al[12]	2001	Brazil	119 (89/30)	Range, 18–60	*D pteronyssinus*	≥4	Der p sIgE	rELISA	3.9 EU/mL
Schuetze[9]	1999	Germany	138 (91/47)	Range, 6–8	*D pteronyssinus* and histamine	≥2	Der p sIgE	ImmunoCAP	0.35 U/mL
Barber et al[8]	2012	Spain	468 (397/71)	Mean (SD), 25.6 (12.4)	*D pteronyssinus*	>3	Der p sIgE	ImmunoCAP	0.35 U/mL

Abbreviations: A/C: case/control; rELISA, reverse enzyme-linked immunosorbent assay; EI, OD of the test sample/cut off; RAST, radioallergosorbent test; sIgE, specific IgE; SPT, skin prick test.
[a]Age information is not available.

the methodologic quality of the eligible studies was adequate and not significantly affected by bias.

Accuracy of Der p 1 and Der p 2 sIgE in the Diagnosis of D Pteronyssinus IgE Sensitization

The results of this meta-analysis are given in Table 2. Compared with the reference standard test, the pooled sensitivity and specificity of Der p 1 sIgE were 0.764 (95% CI, 0.732–0.794) and 0.787 (95% CI, 0.720–0.844), respectively (Fig 3). The pooled sensitivity and specificity of Der p 2 sIgE were 0.804 (95% CI, 0.758–0.844) and 1.000 (95% CI, 0.979–1.000), respectively (Fig 4). The PLR and NLR Der p 1 sIgE were 10.793 (95% CI, 1.664–70.003) and 0.252 (95% CI, 0.144–0.442), respectively. The PLR and NLR of Der p 2 sIgE were 44.882 (95% CI, 13.146–153.238) and 0.248 (95% CI, 0.169–0.365), respectively. The DOR of Der p 1 sIgE and Der p 2 sIgE were 68.471 (95% CI, 5.775–811.76) and 272.96 (95% CI, 71.344–1044.4), respectively. The SROC curve exhibited an AUC of 0.938 (95% CI, 0.889–0.988) and 0.993 (95% CI, 0.986–0.999) (Fig 5), indicating that Der p 1 sIgE and Der p 2 sIgE provide high diagnostic accuracy. We also compared the pretest probability with the posttest probability. The result indicates that the pretest probability is 30% and the posttest probability is 96% and 99% for Der p 1 and Der p 2 sIgE, respectively. This finding means that 2 indicators have high diagnostic values. Subgroup analyses were performed to assess the influence of sample size and publishing time (Table 2). The diagnostic accuracy data were consistent across different subgroups.

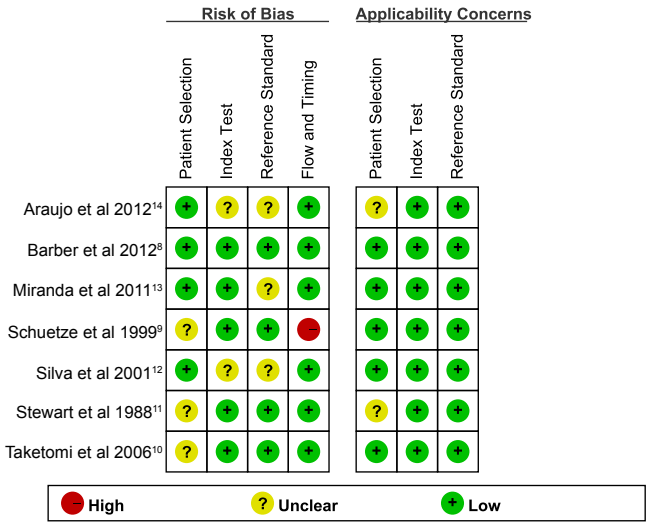

Figure 2. Summary of QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) plot.

Threshold Effect and Heterogeneity

The threshold effect is a major source of between-study heterogeneity. The threshold effect analysis revealed that the Spearman correlation coefficient and *P* were 0.143 and .79 (>.05) and 0.600 and .28 (>.05) for of Der p 1 and Der p 2 sIgE, respectively. This finding suggests that there is no significant threshold effect (Table 2). As shown in the forest plots of accuracy data (sensitivity, specificity, PLR, NLR, and DOR), significant heterogeneity was detected in most variables, with the exception of the PLR and DOR of Der p 2 sIgE. Because meta-regression was not suitable for detecting the source of heterogeneity because the number of studies involved was less than 10, sources of heterogeneity were analyzed via subgroup analysis and the influence exerted by a single study on the pooled effect quantity. Table 3 reveals that in that study[13] Der p 2 sIgE detection in particular contributed to the high level of heterogeneity observed. However, the pooled results were not affected significantly by this study.

Sensitivity Analysis and Publication Bias

A sensitivity analysis was performed, and the results revealed that the pooled results were not significantly affected by the individual studies (Table 3). The publication bias was tested using the Deek's funnel plot, and the results indicate that the funnel plot and *P* value of Der p 1 and Der p 2 sIgE were was 0.19 and .71, respectively. This finding suggests that there is no evidence of publication bias.

Conclusion

Although SPT using crude extract has been performed as a standard test in combination with case history, and it has relative lower cost and higher sensitivity than Der p 1 and Der p 2 sIgE in diagnosis of *D pteronyssinus* IgE sensitization, there are many problems with the method that are worth noting. In many cases, the application of SPT is limited because of the reasons mentioned in the Introduction. In addition, the use of crude allergen may provoke the development of sensitization against additional allergenic proteins in the extract.[50] In contrast, Der p 1 and Der p 2 are allergen components purified from their native sources or produced as recombinant proteins. Measurements of Der p 1 sIgE and

Table 2
Subgroup Analysis and Threshold Effect[a]

	Sensitivity	Specificity	PLR	NLR	DOR	AUC
Der p 1[8–11,13,14]						
Overall	0.764 (0.732–0.794)	0.787 (0.720–0.844)	10.793 (1.664–70.003)	0.252 (0.144–0.442)	68.471 (5.775–811.76)	0.938
Year						
Before 2011	0.761 (0.692–0.821)	0.965 (0.901–0.993)	16.933 (0.658–435.582)	0.276 (0.187–0.407)	63.151 (7.022–567.96)	0.912
2011 or later	0.765 (0.728–0.800)	0.629 (0.525–0.725)	8.264 (0.310–220.325)	0.178 (0.046–0.684)	81.534 (0.701–9484.9)	0.958
Sample size						
Small (<100)	0.863 (0.800–0.912)	0.943 (0.843–0.988)	11.901 (0.881–160.799)	0.136 (0.029–0.632)	124.05 (5.864–2624.4)	0.974
Large (>100)	0.737 (0.699–0.772)	0.723 (0.638–0.798)	11.800 (0.150–926.440)	0.292 (0.133–0.643)	39.110 (0.571–2678.7)	0.794
Der p 2[9,10,12–14]						
Overall	0.804 (0.758–0.844)	1.000 (0.979–1.000)	44.882 (13.146–153.238)	0.248 (0.169–0.365)	272.96 (71.344–1044.4)	0.993
Year						
Before 2011	0.715 (0.644–0.779)	1.000 (0.975–1.000)	66.480 (13.497–327.458)	0.296 (0.237–0.370)	222.77 (43.138–1150.4)	0.737
2011 or later	0.907 (0.851–0.947)	1.000 (0.868–1.000)	25.314 (3.692–173.544)	0.040 (0.000–5.017)	551.01 (15.749–19278.4)	…[b]
Sample size						
Small (<100)	0.866 (0.791–0.921)	1.000 (0.920–1.000)	34.755 (5.004–241.411)	0.058 (0.000–6.851)	547.53 (13.921–21535.3)	…[b]
Large (>100)	0.772 (0.712–0.825)	1.000 (0.972–1.000)	53.278 (10.896–260.511)	0.244 (0.183–0.325)	225.80 (43.544–1170.9)	0.940

Abbreviations: AUC, area under curve; DOR, diagnostic odds ratio; NLR, negative likelihood ratio; PLR, positive likelihood ratio.
[a]Data are presented as accuracy data with 95% confidence intervals. Der p 1: Spearman correlation coefficient of 0.143 ($P = .79$), and Der p 2: Spearman correlation coefficient of 0.600 ($P = .28$).
[b]Too few studies to obtain results.

Der p 2 sIgE had higher diagnostic specificity.[3] With the development of modern biochemistry technology, the availability of these purified or recombinant proteins is not an issue. Thus, the detection of Der p 1 and Der p 2 sIgE has attracted more and more attention as a possible diagnosis method for *D pteronyssinus* IgE sensitization. There are many reports about the diagnostic value of serum Der p 1 and Der p 2 sIgE testing for *D pteronyssinus* IgE sensitization. Thus, we performed this meta-analysis and systematic review to determine the diagnostic accuracy of Der p 1 and Der p 2 sIgE for *D pteronyssinus* IgE sensitization detection. The sensitivity and specificity of Der p 1 and Der p 2 sIgE are high enough for use as diagnostic methods. It is worth noting that the high DOR and AUC are indicative of an overall high diagnostic accuracy for Der p 1 and Der p 2 sIgE. Because a feasible biomarker with optimal

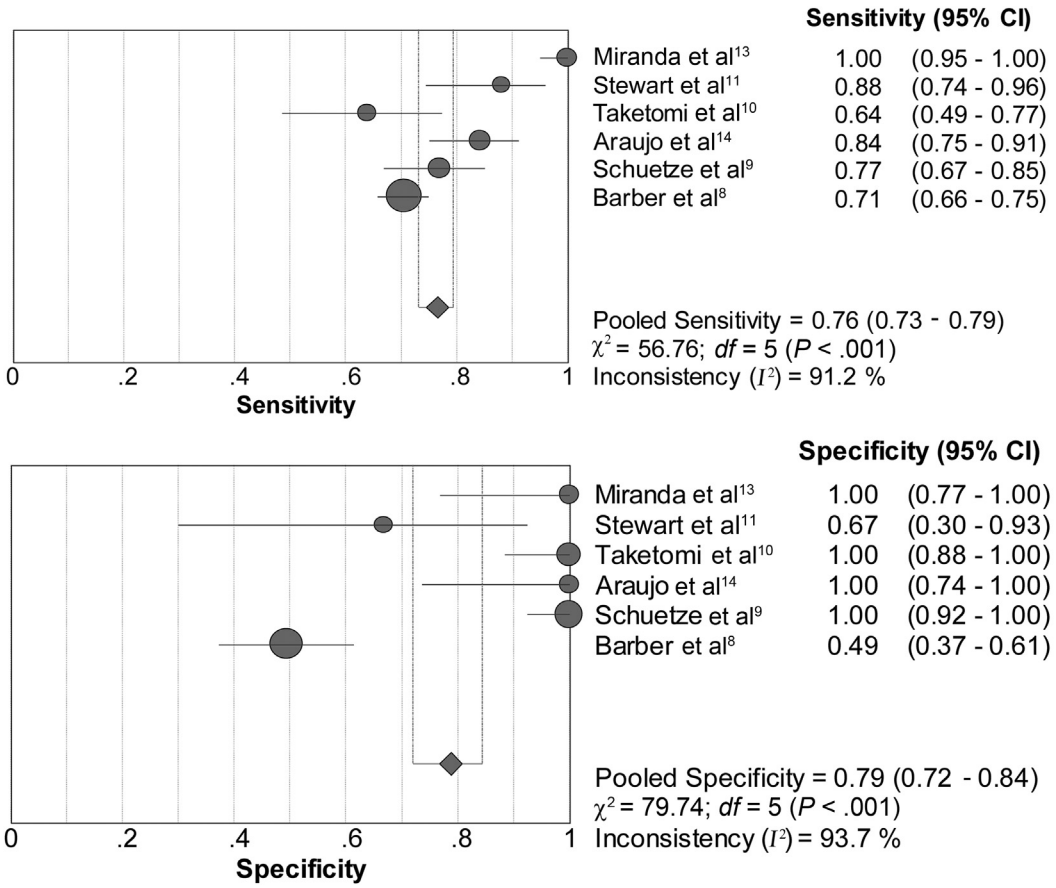

Figure 3. Forest plot of sensitivity and specificity of Der p 1 specific (IgE). The pooled sensitivity was 0.764 (95% confidence interval [CI], 0.732–0.794), and the pooled specificity was 0.787 (95% CI, 0.720–0.844).

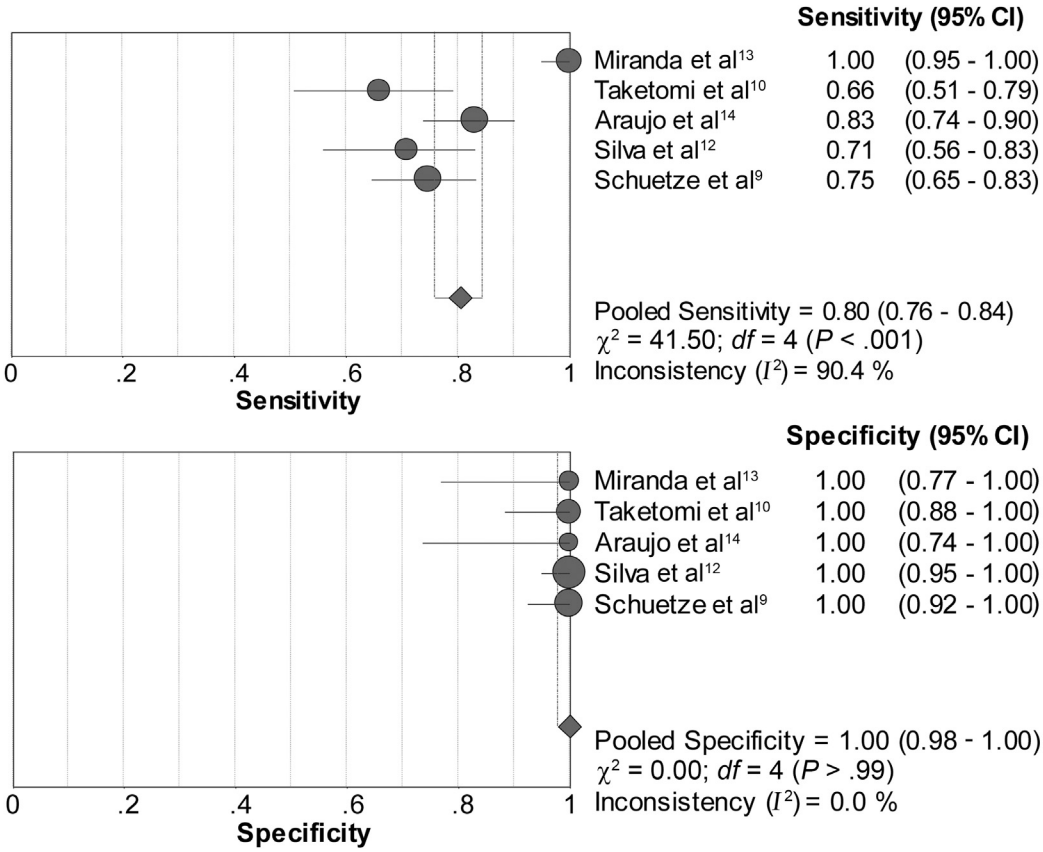

Figure 4. Forest plot of sensitivity and specificity of Der p 2 specific IgE. The pooled sensitivity was 0.804 (95% confidence interval [CI], 0.758–0.844), and the pooled specificity was 1.000 (95% CI, 0.979–1.000).

performance is needed and it was previously unclear whether Der p 1 and Der p 2 sIgE provide sufficient diagnostic accuracy, this meta-analysis adds important evidence to the body of literature.

This is the first meta-analysis, to our knowledge, of the diagnostic performance of Der p 1 and Der p 2 sIgE used for the diagnosis of *D pteronyssinus* IgE sensitization and represents an attempt to provide guidance for future studies. However, the limitations of this meta-analysis should also be highlighted. First, several of the studies analyzed were small scale, which might lead to bias. To evaluate the effects of small-scale studies on the overall results, subgroup and sensitivity analyses were performed; the results revealed that the pooled results were stable and not affected by bias. Second, significant heterogeneity was observed. Because the number of studies included in this analysis is less than 10, a

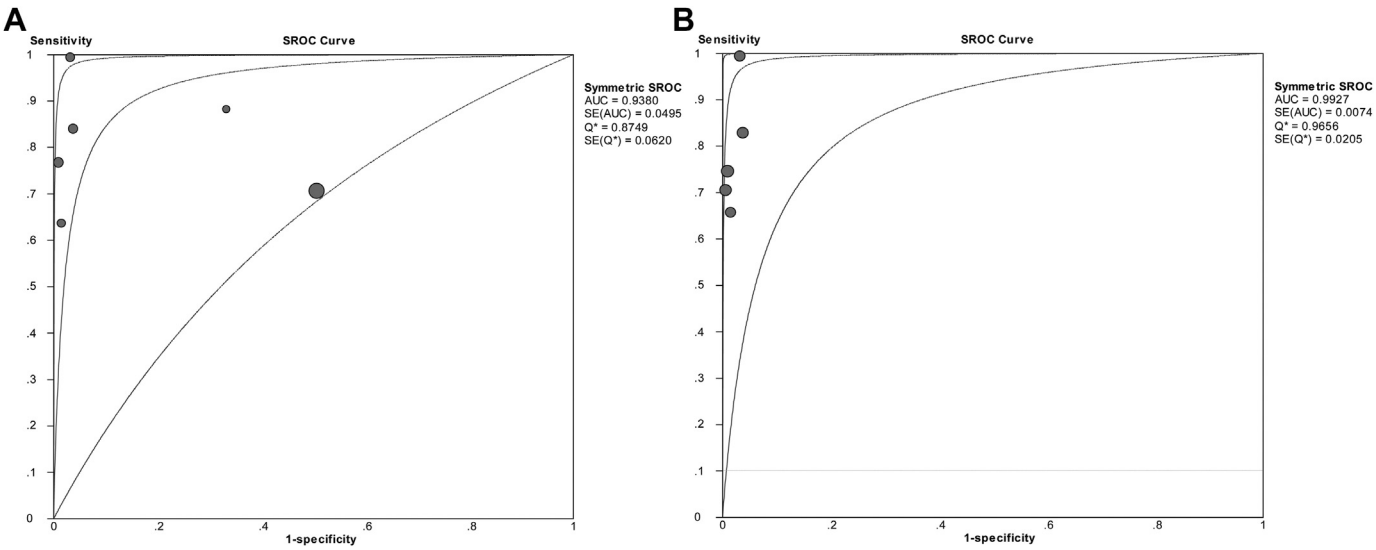

Figure 5. The summary receiver operating characteristic (SROC) curve indicated high diagnostic accuracy. A, Der p 1 specific IgE; B, Der p 2 specific IgE. AUC indicate area under the curve.

Table 3
Meta-analysis Estimates

Omitted Study	Year	Sensitivity (95% CI)	Specificity (95% CI)	Heterogeneity (*P* value, I^2)	
				Sensitivity	Specificity
Der p 1					
Miranda et al[13]	2011	0.739 (0.704–0.772)	0.769 (0.698–0.830)	.003, 74.5%	<.001, 94.5%
Stewart et al[11]	1988	0.757 (0.724–0.789)	0.793 (0.725–0.851)	<.001, 92.4%	<.001, 94.9%
Taketomi et al[10]	2006	0.773 (0.740–0.804)	0.745 (0.668–0.812)	<.001, 92.4%	<.001, 93.7%
Araujo et al[14]	2012	0.753 (0.718–0.786)	0.772 (0.702–0.833)	<.001, 92.5%	<.001, 94.6%
Schuetze et al[9]	1999	0.764 (0.729–0.796)	0.713 (0.629–0.787)	<.001, 93.0%	<.001, 92.5%
Barber et al[8]	2012	0.833 (0.789–0.871)	0.973 (0.924–0.994)	<.001, 90.0%	<.001, 75.3%
Der p 2					
Miranda et al[13]	2011	0.753 (0.697–0.803)	1.000 (0.977–1.000)	.12, 48.0%	>.99, 0.00%
Taketomi et al[10]	2006	0.827 (0.779–0.868)	1.000 (0.975–1.000)	<.001, 91.5%	>.99, 0.00%
Araujo et al[14]	2012	0.795 (0.740–0.842)	1.000 (0.977–1.000)	<.001, 92.7%	>.99, 0.00%
Silva et al[12]	2001	0.819 (0.771–0.861)	1.000 (0.965–1.000)	<.001, 92.2%	>.99, 0.00%
Schuetze et al[9]	1999	0.824 (0.772–0.869)	1.000 (0.971–1.000)	<.001, 92.3%	>.99, 0.00%

Abbreviation: CI, confidence interval.

multivariate meta-regression was not performed. However, the Spearman correlation suggested that the heterogeneity was not caused by a threshold effect. Through single-study omission analysis, we found that this study[13] is the primary source of heterogeneity, especially in Der p 2 sIgE detection. However, the pooled results of the analyses of sensitivity and specificity were consistent whether the study was eliminated or not. Third, only English databases were searched in this meta-analysis, but there are maybe many eligible studies conducted in non–English-speaking countries. Thus, it was possible that there were some non-English studies that were not included in this meta-analysis.

In conclusion, in our meta-analysis of 7 studies that included 1040 participants, detection of Der p 1 and Der p 2 sIgE in serum appears to be of adequate diagnostic value for use in detecting *D pteronyssinus* IgE sensitization. In addition to their high specificity and noninvasive nature, this serum IgE detection is convenient to patients with allergy symptoms and causes fewer adverse effects than SPTs. There is little limitation in the use of this method. In addition, in vitro diagnostics through collection of the patients' blood and detection with modern equipment in the specialized laboratory are more standardized and objective. More meaningful is if all allergen (not only *D pteronyssinus*) sensitization can be tested by serum sIgE, just like Der p 1 and Der p 2 sIgE, once venous blood collection can replace numbers of SPTs. Therefore, Der p 1 and Der p 2 sIgE might be promising screening tests for *D pteronyssinus* IgE sensitization. Patients with positive results may receive specific desensitization therapy. Patients with negative results with obvious allergy symptoms can use another method for diagnosis, such as *D pteronyssinus* extract SPTs. Minami et al[5] also reported that IgE to Der p 1 and Der p 2 were highly predictive of allergen-induced immediate asthmatic response. These findings validate the clinical utility of measuring the levels of IgE to Der p 1 and Der p 2 as a diagnostic tool for *D pteronyssinus* IgE sensitization.[5] Despite the small number of studies and the presence of high heterogeneity, the diagnosis performance of these 2 indicators is stable. Thus, Der p 1 and Der p 2 sIgE may be suitable diagnostic tools for *D pteronyssinus* IgE sensitization. On the basis of the results of the meta-analysis, Der p 2 sIgE has a higher diagnostic value than Der p 1 sIgE (Table 2). Although this in vitro test has many advantages, there are still FN results, which could result in a misdiagnosis. Improving the in vitro diagnostic level to reduce the FN rate is also an ongoing challenge. A combination of Der p 1 and Der p 2 allows for the diagnosis of more than 95% of patients with *D pteronyssinus* IgE sensitization.[37] If more important antigenic proteins are combined into the in vitro diagnostic system, it will greatly enhance the diagnostic sensitivity then significantly reduce the FN rate. However, this meta-analysis cannot provide evidence supporting these conclusions because only one study provided the raw data for the combination of Der p 1 and Der p 2 sIgE detection. Many articles did not provide the original data, and we have not received replies to our requests for the original data. Thus, more persuasion or more standard original research and reliable data are required. If more original data on diagnosis accuracy of combination of Der p 1 and Der p 2 sIgE are available, another meaningful systematic review may be performed.

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