

The role of serum periostin in the diagnosis of asthma: A meta-analysis

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ABSTRACT

Background: Serum periostin has been proposed as a noninvasive biomarker for asthma diagnosis and management. However, its accuracy for the diagnosis of asthma in different populations is not completely clear.

Methods: This meta-analysis aimed to evaluate the diagnostic accuracy of periostin level in the clinical determination of asthma. Several medical literature data bases were searched for relevant studies through December 1, 2019. The numbers of patients with true-positive, false-positive, false-negative, and true-negative results for the periostin level were extracted from each individual study. We assessed the risk of bias by using Quality Assessment of Diagnostic Accuracy Studies 2. We used the meta-analysis to produce summary estimates of accuracy.

Results: In total, nine studies with 1757 subjects met the inclusion criteria. The pooled estimates of sensitivity, specificity, and diagnostic odds ratios for the detection of asthma were 0.58 (95% confidence interval [CI], 0.38–0.76), 0.86 (95% CI, 0.74–0.93), and 8.28 (95% CI, 3.67–18.68), respectively. The area under the summary receiver operating characteristic curve was 0.82 (95% CI, 0.79–0.85). And significant publication bias was found in this meta-analysis ($p = 0.39$).

Conclusion: Serum periostin may be used for the diagnosis of asthma, with moderate diagnostic accuracy.

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Asthma is one of the most frequent chronic inflammatory diseases, with many clinical phenotypes in both adults and children.¹ It is characterized by paroxysmal or persistent respiratory symptoms associated with variable airflow obstruction, airway hyperresponsiveness, and underlying inflammation.^{1,2} The current criterion standard for a diagnosis of asthma is based on the history of recurrent respiratory symptoms, a variable expiratory airflow limitation, and respiratory function testing.^{3,4} The aim of the present meta-analysis was to evaluate the objective tests and to determine the best strategy for diagnosing asthma.

Periostin is a secreted extracellular matrix protein that was originally isolated from osteoblasts and periosteum.⁵ It is a 90-kDa protein whose expression can be induced by type 2 inflammatory cytokines interleukin-4 and interleukin-13 in the lung epithelial cells and in fibroblasts.^{6,7} Interleukin-13 induces the secretion of periostin from airway epithelial cells. Periostin plays a role in airway fibrosis and infiltration of the tissues by the eosinophils, which is thought to promote airway remodeling in

patients with asthma.^{6,7} Periostin is widely recognized as a biomarker associated with specifically T2 inflammation. Recently, several recent studies reported that serum periostin could be a candidate biomarker for asthma.^{8–10}

Although periostin is easy to measure in serum, it can also be produced by bone, connective, myocardial, skin, and lung tissue^{7,11}; therefore, its diagnostic efficacy lacks specificity and is of limited application.¹¹ Indeed, evidence of the diagnostic efficacy of serum periostin is accumulating.^{12–17} However, according to their results,^{12–17} this opinion on the diagnostic role of serum periostin in patients with asthma is still controversial.^{8,15} Therefore, it is necessary to perform a meta-analysis to comprehensively and systematically understand the diagnostic accuracy of serum periostin in asthma. To our knowledge, there is no meta-analysis focused on the diagnostic value of periostin for asthma. In this study, we aimed to evaluate the diagnostic accuracy of periostin in the clinical determination of asthma.

METHODS

Literature Search and Study Identification

We conducted a systematic literature search of four data bases, which included PubMed (Bethesda, MD), Embase (London, UK & Amsterdam, Netherlands), the Cochrane Library (John Wiley & Sons, Hoboken, USA) and Web of Science (Institute for Scientific Information, Philadelphia), from each data base's inception to December 1, 2019. The search was specifically tailored to each of the electronic data bases. Search terms included periostin and asthma. In addition, we

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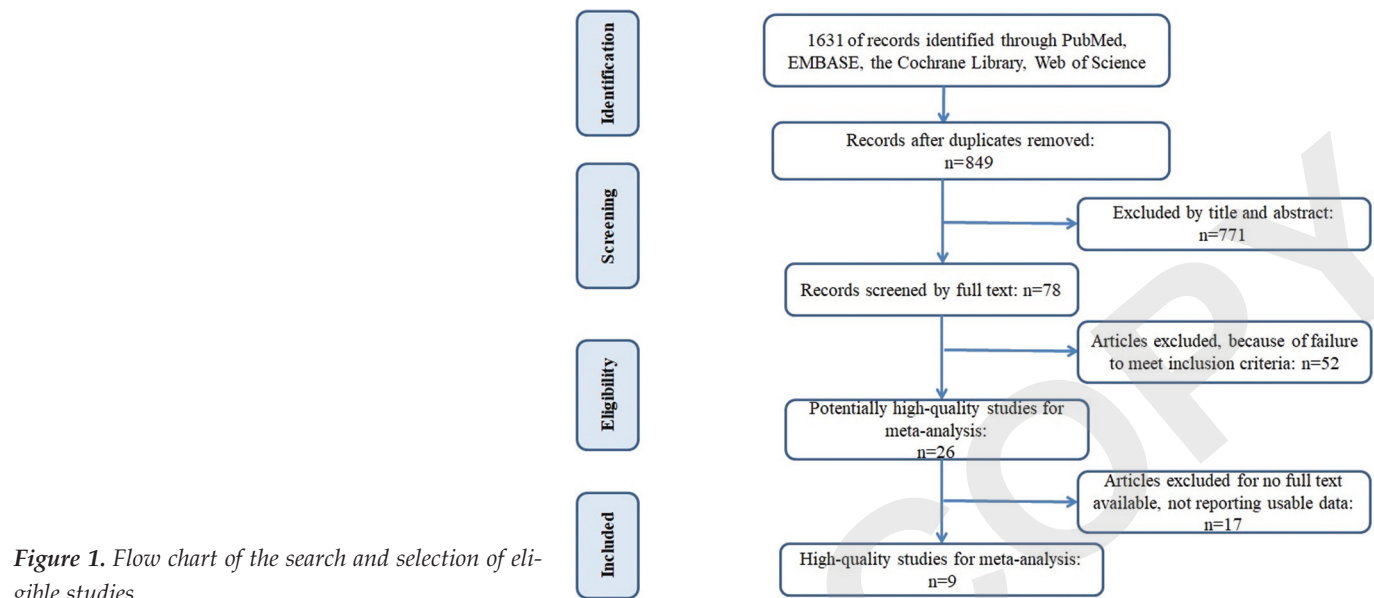


Figure 1. Flow chart of the search and selection of eligible studies.

conducted supplementary searches of the references of the retrieved articles. Inclusion criteria for eligible studies were as follows: (1) diagnosis test study design, (2) the index test was periostin, and (3) sufficient data to reconstruct a two-by-two contingency table for meta-analysis. Studies were excluded if one of the following existed: (1) the article was a review, case report, or editorial comment; (2) studies were conducted on animals or *in vitro* systems; (3) duplicate publication; and (4) necessary data could not be obtained. Two investigators (L.Y., Q.Z.) independently screened all the studies for suitability for inclusion. Any disagreement was resolved by discussion with a third investigator (S.W.). L. Yang and Q. Zhao are the co-first authors. Study selection is summarized in Fig. 1.

Quality Assessment

We used the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool to assess the quality of each included study. QUADAS-2 comprises four domains: patient selection, index test, reference standard, and flow and timing. These four domains were used for evaluating the risk of bias, and the first three domains were applied to assess applicability by indicating a “low,” “unclear,” or “high” rating. The quality assessment was conducted independently by two investigators (L.Y., Q.Z.).

Data Extraction

Characteristic information of included studies were extracted, including first author, country, year of publication, sample size, and cutoff value of periostin in each study. Absolute numbers of true-positive (TP), false-positive (FP), false-negative (FN), and true-negative (TN) results were also extracted.

Statistical Analyses: Data Analysis

A meta-analysis of included studies was carried out with Stata 13.0 (StataCorp LP, College Station, TX). By using bivariate meta-analysis, the pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratios (DOR) were calculated. A summary receiver operating characteristic curve (SROC) was generated, and the area under the curve (AUC) and the Q index were then calculated appropriately. The Cochran Q and χ^2 tests were used to determine heterogeneity caused by others factors. A value of $I^2 > 50\%$ was defined as heterogeneity. A p value of <0.05 was considered statistically significant. Meta-regression was used to analyze heterogeneity. The sensitivity analysis was conducted to determine whether our assumptions had a major effect on the results of the review. The Deeks funnel plot asymmetry analysis test was performed to investigate the publication bias.¹⁸ RevMan software (version 5.3; Cochrane Collaboration, Oxford, United Kingdom) was used to make the quality assessment graph of the risk of bias and applicability concerns.

RESULTS

Search Results

After assessment of the full texts, nine studies met our inclusion criteria and were included in this meta-analysis.^{8–10,12–17} Coincidentally, the nine articles were all from Asian countries. There were 1757 subjects, including adults and children. All the patients were diagnosed as having asthma. The diagnostic criterion standard included symptoms, pulmonary function testing, guidelines for asthma, and laboratory results. The control groups in all the studies were identified as healthy people or children without asthma. A flow diagram of

Table 1 Summary of the diagnostic results of the included studies

Study, y	Country	Study Design	No. Patients (no. asthma patients/no. controls)	Age	Control	Cutoff Value, ng/mL	Diagnostic Results, no.				Sensitivity	Specificity
							TP	FP	FN	TN		
Lee <i>et al.</i> , ¹⁰ 2018	Korea	Retrospective	136 (53/83)	Adult	Healthy	89.5	34	10	19	73	83	94
Takahashi <i>et al.</i> , ¹⁶ 2018	Japan	Retrospective	439 (235/204)	Adult	Healthy	97	146	55	89	149	62	73
Wang <i>et al.</i> , ¹³ 2018	China	Retrospective	174 (124/50)	Adult	Healthy	85.92	37	9	87	41	30	82.26
Li <i>et al.</i> , ¹⁴ 2017	China	Retrospective	115 (65/50)	Children	Healthy	80.89	19	4	46	46	29.2	92
Emprn <i>et al.</i> , ⁸ 2016	India	Prospective	101 (71/30)	Adult	Healthy	24.6	69	4	2	26	97.2	86.7
Inoue <i>et al.</i> , ⁹ 2016	Japan	Retrospective	55 (28/27)	Children	Children without asthma	117	21	11	7	16	75	59.3
Song <i>et al.</i> , ¹² 2015	Korea	Retrospective	83 (54/29)	Children	Healthy	90	15	1	39	28	28	97
Kim <i>et al.</i> , ¹⁵ 2014	Korea	Retrospective	364 (277/87)	Adult	Healthy	54.5	199	32	78	55	71.8	63.2
Kanemitsu <i>et al.</i> , ¹⁷ 2013	Japan	Retrospective	290 (224/66)	Adult	Healthy	95	85	1	139	65	37.9	98.5

TP = True positive; FP = false positive; TN = true negative; FN = false negative.

the selection process is shown in Fig. 1. Characteristics of the included studies are displayed in Table 1. Among the nine trials published from 2013 to 2018, only one trial was prospective and the other eight were retrospective. All of the studies were from Asian countries: three studies from Japan, three studies from Korea, two studies from China, one study from India. The count data for primary studies, including TP, FP, FN, and TN results were extracted and are presented in Table 1.

Quality Assessment

A quality assessment of the included studies was performed by using QUADAS-2 criteria. Detailed results of the QUADAS-2 assessment are provided in Fig. 2. The quality evaluation was performed independently by two investigators (L.Y., Q.Z.).

Diagnostic Accuracy Analysis

Results of the meta-analysis indicated that serum periostin was a useful test for diagnosing asthma. The pooled sensitivity for serum periostin was 0.58 (95% confidence interval [CI], 0.38–0.76), whereas the pooled specificity for serum periostin was 0.86 (95% CI, 0.74–0.93) (Fig. 3). The pooled DOR was 8.28 (95% CI, 3.67–18.68). Moreover, an SROC was also constructed for periostin and the AUC was 0.82 (95% CI, 0.79–0.85) (Fig. 4). The combined PLRs and combined NLRs are 4.06 (95% CI, 2.32–7.12) and 0.49 (95% CI, 0.32–0.76), respectively, which further suggested that serum periostin has sufficient power to confirm or exclude asthma. The Fagan nomogram analysis showed that, with a pooled PLR of 4 and a fixed pretest probability of 20%, the posttest probability was increased to 50%. Conversely, with a combined NLR of 0.49, the posttest probability was decreased to 11% (Fig. 5). The pooled positive predictive value (PPV) and negative predictive value (NPV) in this meta-analysis was 87 (95% CI, 77–93) and 56 (95% CI, 41–70), respectively.

When analyzing these studies, the sensitivity of serum periostin for a diagnosis of asthma in children was 37.4 (95% CI, 29.6–45.8) and the specificity was 84.9 (95% CI, 76.6–91.1). The DOR was 5.10 (95% CI, 2.39–10.89). For the diagnosis of asthma in adults, the pooled sensitivity for serum periostin was 0.65 (95% CI, 0.40–0.84), whereas the pooled specificity for serum periostin was 0.85 (95% CI, 0.71–0.92). The DOR was 10.35 (95% CI, 3.21–33.40). In the article by Lee *et al.*,¹⁰ both subjects with nonoccupational asthma and subjects with asthma to Toluene diisocyanate are considered. Periostin levels are significantly lower in patients with nonoccupational asthma.¹⁰ In our study, the pooled estimates of sensitivity, specificity, DOR, and SROC for the detection of asthma were 0.57 (95% CI, 0.35–0.77), 0.86 (95% CI, 0.72–0.93), 7.95 (95% CI, 3.16–



Figure 2. Presentation of Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) results.

20.05), and 0.82 (95% CI, 0.78–0.85) after exclusion of the article by Lee *et al.*¹⁰

Heterogeneity and Meta-Regression Analysis

As shown by the forest plot of the pooled main diagnostic measures (sensitivity and specificity) in Fig. 3, there was significant heterogeneity for serum periostin in the asthma diagnosis (sensitivity $I^2 = 95.79\%$, $p < 0.05$; specificity $I^2 = 86.95\%$, $p < 0.05$, respectively). The Spearman rank correlation coefficient was 0.617 ($p = 0.08$), which demonstrated that the heterogeneity was not caused by the threshold effect. A meta-regression analysis was used to identify the sources of heterogeneity of the following aspects: study design, age, sample size, and cutoff value. None of these factors were obvious sources of heterogeneity.

Sensitivity Analysis

A sensitivity analysis was conducted, and one outlier was found (Fig. 6). After exclusion, the I^2 for heterogeneity decreased both in sensitivity (from 95.79 to 92.24%) and specificity (from 86.95 to 86.72%). The overall results showed only minimal changes and were similar to the original ones (sensitivity 0.58 and specificity 0.86). When combined with goodness-of-fit and bivariate normality analyses, we confirmed the robustness of our meta-analysis.

Publication Bias

We performed a Deeks funnel plot asymmetry test to investigate publication bias in this meta-analysis.¹⁸ The

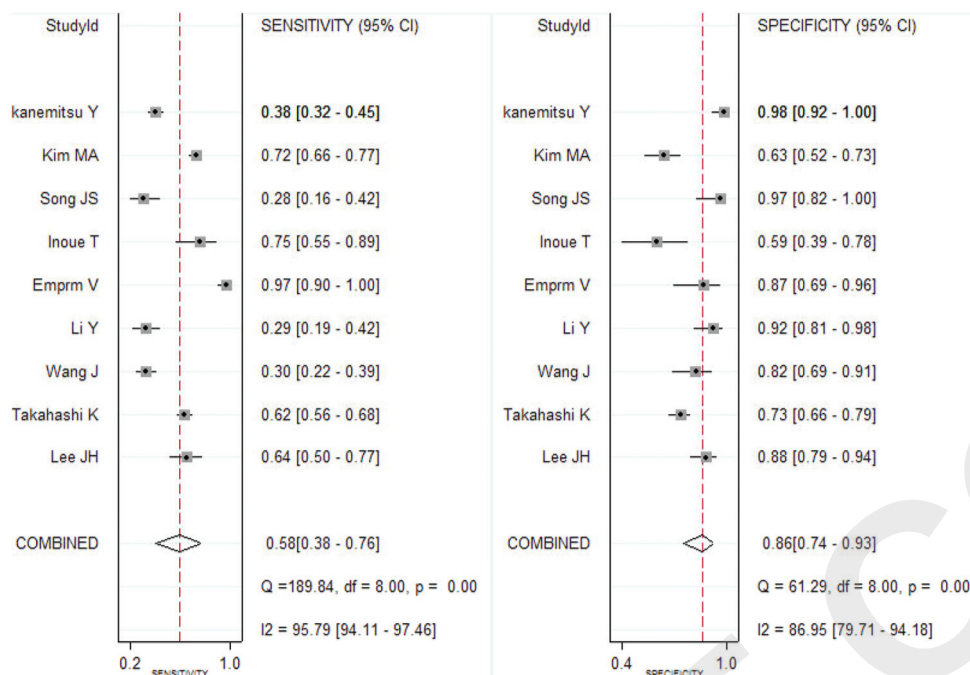


Figure 3. Forest plots, showing the sensitivity and specificity of periostin in the diagnosis of asthma.

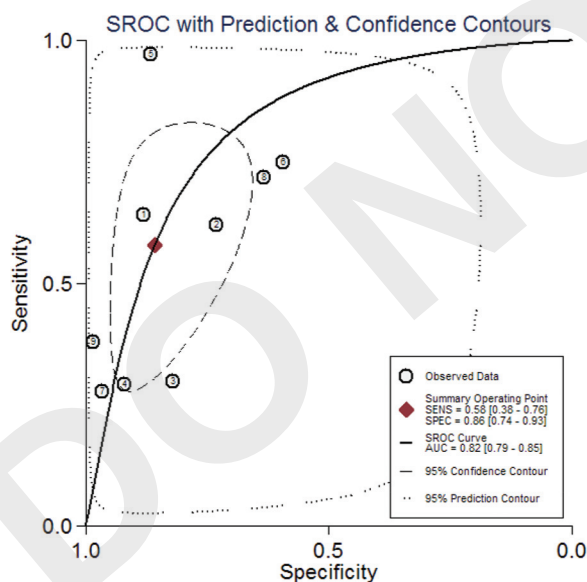


Figure 4. Summary receiver operating characteristic curve of periostin in the diagnosis of asthma.

funnel plots for publication bias showed no asymmetry (Fig. 7). The slope was not significant ($p = 0.39$), and no publication bias was detected.

DISCUSSION

This meta-analysis was a systematic review that summarized the diagnostic accuracy of using serum periostin in identifying patients with asthma. We identified nine current diagnostic accuracy studies,

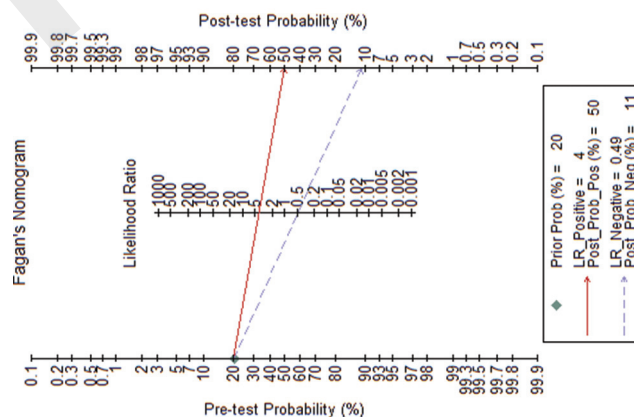


Figure 5. Fagan nomogram plot analysis to evaluate the clinical utility of periostin for the detection of asthma.

including 1757 subjects with asthma, and all the studies used the standardized QUADAS-2 framework. This analysis showed that serum periostin had a moderate sensitivity, specificity, and DOR for a diagnosis of asthma. These results demonstrated that serum periostin was of moderate diagnostic value for asthma.

A recent systematic review and meta-analysis included nine studies and 1448 subjects to pool results in determining the effectiveness of periostin in detecting asthma.¹⁹ The pooled sensitivity, specificity, and DOR were 0.68 (95% CI, 0.42–0.86), 0.87 (95% CI, 0.76–0.93), and 13.78 (95% CI, 4.64–40.93), respectively; the area under the SROC was 0.87 (95% CI, 0.84–0.90).¹⁹ Because Jia X, et al. chose chronic obstructive pulmonary disease as the control group, the bias caused by

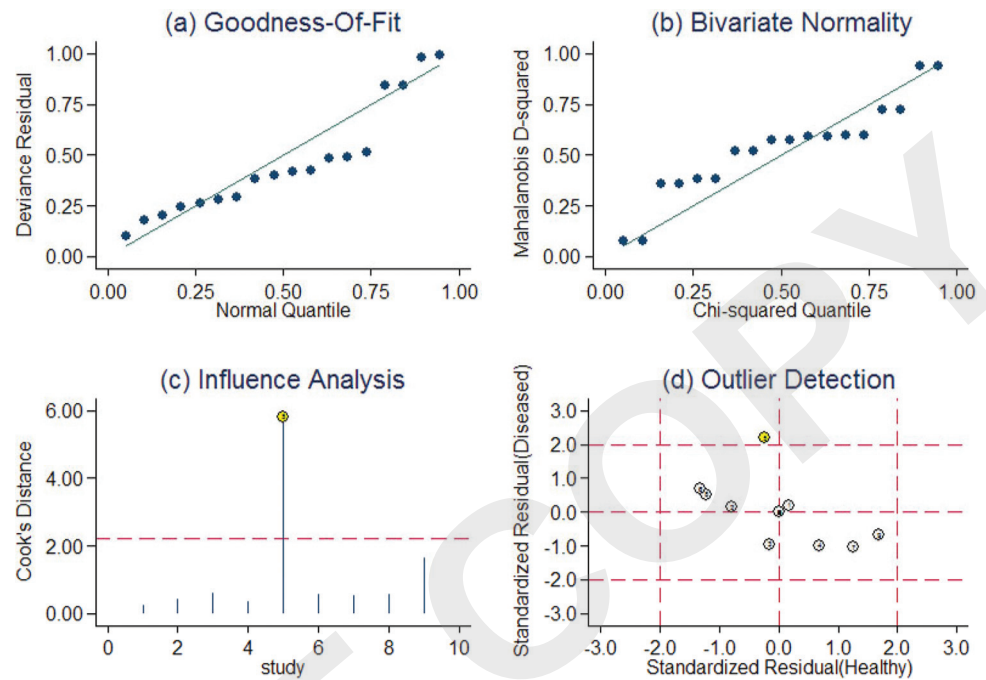


Figure 6. Sensitivity analysis: (a) graphic depiction of residual-based goodness of fit, (b) bivariate normality, and (c) influence and (d) outlier detection analyses.

the selection bias could not be ruled out.¹⁹ The control groups in all the studies were identified as healthy people or children without asthma in our analysis. The cases in our analysis were limited to assessing serum periostin; peripheral blood is more accessible and repeated than bronchial mucosa samples. In subgroup analysis, serum periostin showed different pooled sensitivity and specificity in populations of children and adults. The disadvantage of using serum periostin as a biomarker is that basal levels of serum periostin in childhood are high and vary, depending on bone growth.²⁰

Periostin may also be elevated in diseases that are often associated with asthma, such as rhinosinusitis and atopic dermatitis.^{21–23} There might be differences between published and unpublished studies. Although the Deeks funnel plot showed that our meta-analysis did not produce publication bias ($p=0.39$), we could not completely exclude the impact of unpublished articles.

A recent meta-analysis included 25 studies to pool results in assessing the diagnostic value of fractional exhaled nitric oxide (FeNO) in detecting asthma.²⁴ The sensitivity, specificity, and DOR for the entire population were 0.72 (95% CI, 70–74%), 0.78 (95% CI, 76–80%), and 15.92 (95% CI, 10.70–23.68), respectively. The SROC analysis revealed a receiver operating characteristic of 0.88. The results of our meta-analysis indicated that the pooled sensitivity and specificity of serum periostin were 0.58 (95% CI, 0.38–0.76) and 0.86 (95% CI, 0.74–0.93), respectively. This meant that 58% of the patients with asthma had high serum periostin levels, and 86% of the population

without asthma had low serum periostin levels. Thus, serum periostin has higher specificity compared with conventional FeNO.

The values of sensitivity, specificity, and area under the ROC curve that are closer to 1 are preferred. Glas *et al.*²⁵ found that the DOR combines the strengths of sensitivity and specificity as the prevalence in dependent indicators and has the advantage of accuracy over a single indicator. The value of a DOR ranges from 0 to infinity, and the higher values indicate better diagnostic efficacy.^{26,27} The DOR value of 8.28 demonstrates that serum periostin could be a useful biomarker for a diagnosis of asthma. AUC is calculated to evaluate the accuracy of the selected indicator, and SROC is usually used to summarize overall test performance.^{28,29} To indicate excellent accuracy, the value of AUC should be >0.97 .

According to a criterion of Jones *et al.*,²⁷ AUC > 0.97 , 0.93–0.96, 0.75–0.92, and 0.5–0.75 were interpreted as excellent, very good, good, and reasonable, respectively. In this meta-analysis, we showed that serum periostin demonstrates moderate accuracy in the diagnosis of asthma, with an area under the ROC curve of 0.82. NLR and PLR are more meaningful indicators of diagnostic accuracy. According to Grimes *et al.*²⁹ NLRs in the range of 0.2–0.5, 0.2–0.1, and <0.1 represent small, moderate, and large decreases of probability, respectively, when the test result is negative. Similarly, PLRs in the range of 2–5, 5–10, and >10 represent small, moderate, and large increases of probability, respectively, when the test result is positive.

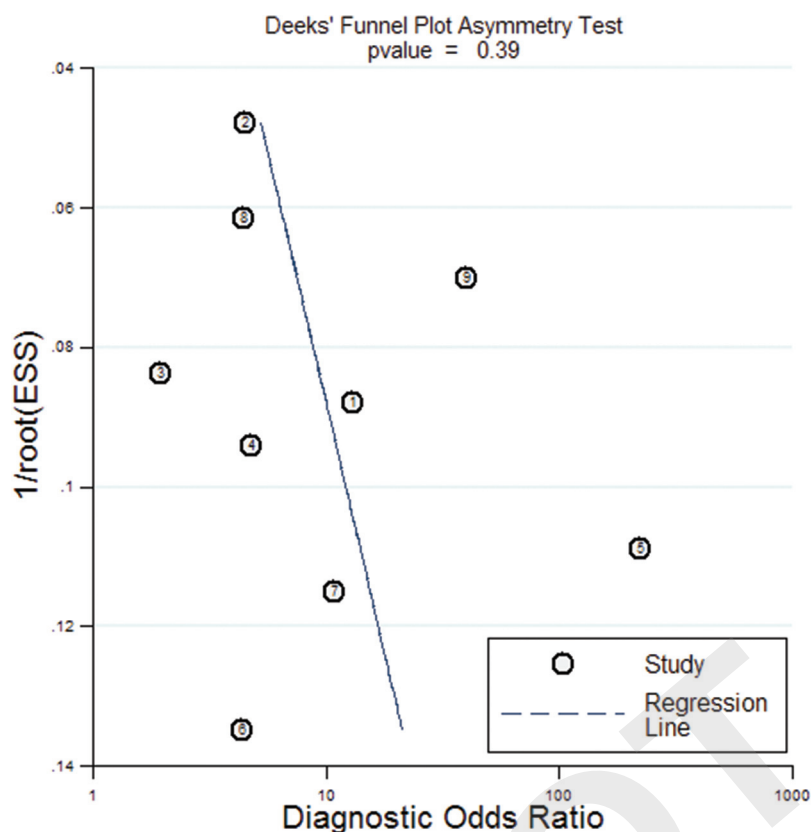


Figure 7. Deeks funnel plot for detecting publication bias.

A good diagnostic test may have a low NLR (NLR < 0.2) and high PLR (PLR > 10). However, the NLR and PLR value of this meta-analysis did not meet these thresholds. In this meta-analysis, an NLR value of 0.49 revealed that patients with asthma had a 49% chance of testing negative, and this method, therefore, is not sensitive enough to rule out asthma in the case of a negative test result. However, a PLR value of 4.06 demonstrated that patients with asthma had a four times higher chance of testing positive than the population without asthma. Based on the current pooled evidence, using serum periostin will help to diagnose asthma but may not fully replace other routine diagnostic methods such as assessing FeNO^{24,26,30-32} and eosinophil values,^{4,30,33} which have been used for the diagnosis of asthma.

Heterogeneity is a potential problem that may affect the interpretation of the results of all meta-analyses. High heterogeneity ($I^2 = 100\%$; $p < 0.05$) was observed for the overall accuracy of serum periostin in asthma diagnosis. One of the primary causes of heterogeneity in test accuracy studies is a threshold effect. Because different diagnostic thresholds were used among the nine studies, we used the Spearman correlation coefficient to analyze the threshold effect. Although the cut-off ranged from 24.6 to 117 ng/mL, the Spearman value indicated that there was no diagnostic threshold effect in this meta-analysis.

The presence of heterogeneity may result from many other factors, including the choice of the criterion standard, age distribution, diet, long-term inhaled corticosteroid use, and so on. More clinical data are needed to identify the sources of heterogeneity. Our analysis showed that the study by Lee *et al.*¹⁰ might be heterogeneous compared with other studies, which was possibly because the case group from this study was of patients with occupational asthma caused by toluene diisocyanate. The subjects with occupational asthma had significantly higher levels of periostin than subjects without occupational asthma. Among the nine studies included, Kanemitsu *et al.*¹⁷ studied patients with asthma treated with long-term inhaled corticosteroid. There is research that hormone therapy may lead to a decline of periostin levels.³⁴

Our study should be interpreted cautiously because several limitations exist in this meta-analysis. First, the final inclusion results showed that the nine articles were all from Asian countries; therefore, publication bias cannot be excluded. Second, the sample size in this meta-analysis was relatively small. Therefore, the results of the trials in a pooled analysis were not robust. More studies are needed for future analyses. Third, high heterogeneity was found in the outcomes of sensitivity, specificity, and DOR, but we failed to identify the main source of high heterogeneity because the information reported was limited.

CONCLUSION

The present meta-analysis provided evidence that serum periostin may be used for the diagnosis of asthma, with moderate diagnostic accuracy. This is the latest meta-analysis to assess the diagnostic value of serum periostin for asthma. More well-designed research studies are needed to further elucidate serum periostin for diagnosis indicator of asthma.

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