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REVIEW



Diagnostic accuracy of periostin in predicting asthma: a systematic review and Meta-analysis

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ABSTRACT

Objective: We sought to evaluate the accuracy of periostin for the diagnosis of asthma through a systematic review and meta-analysis.

Methods: we searched the electronic databases (PubMed, EMBASE, Web of science) to find relevant studies through December 31, 2018. Studies selecting, data extraction and quality assessment were conducted by two researchers independently according to inclusion and exclusion criteria. We used bivariate mixed effects model to conduct the meta-analysis.

Results: A total of 9 studies including 1448 subjects with asthma were analyzed. The pooled sensitivity, specificity, diagnostic odds ratio (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 summary receiver operating curves (SROC) was 0.87 (95% CI, 0.84–0.90). The Spearman correlation coefficient indicated that no threshold effect existed in the included studies. The study design had statistical significance for sensitivity results ($p < 0.001$) through regression analysis. Heterogeneity might be caused by non-threshold effect.

Conclusion: Periostin has moderate accuracy in the diagnosis of asthma.

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KEYWORDS

Periostin; asthma; diagnosis accuracy; meta-analysis

Introduction

Asthma is a chronic inflammatory disease, which is mainly mediated by eosinophils, mast cells and Th2 cells (1). Existing biomarkers useful for asthma diagnosis included eosinophil counts, serum total IgE, pulmonary function test, bronchial provocation test or diastolic test and fractional exhaled nitric oxide (FeNO) (2). However, respiratory symptoms in asthma patients are not typical. Pulmonary function tests are more expensive and bronchial provocation tests have a risk of bronchospasm. These methods cannot comprehensively diagnose asthma with different phenotypes, which may lead to missed diagnosis and misdiagnosis. Therefore, we need more accurate and rapid methods to support clinical diagnosis and treatment better.

Periostin was found to be a marker of Th2-associated inflammation in asthmatic patients (3). It can be used as a potential predictor of airway eosinophilia (4). At the same time, serum periostin level was also helpful to determine the effectiveness of OMALIZUMABin the treatment of asthma (5).

Periostin is an extracellular matrix protein that can be induced by epithelial cells stimulated by the Th2 inflammatory cytokines IL-4 and IL-13 and TGF β , which play an important role in the development of airway fibroblasts and promoting airway remodeling (6). Th2 mediated eosinophilic airway inflammation is a major feature of asthma. Existing studies had shown that the level of serum periostin in eosinophilic asthma patients was higher than that in non-eosinophilic asthma patients (7). Another cohort study based on large sample data showed that high levels of serum periostin were associated with decreased pulmonary function in asthmatic patients (8). Compared with other biomarkers (such as serum total IgE level, blood eosinophil count and the level of FeNO), periostin was the best single predictor of eosinophilic airway inflammation (4). The expression of periostin in airway epithelial cells was also higher in asthmatic patients (9). However, there is no unified conclusion on the value of periostin in the diagnosis of asthma.

This article aims to review the accuracy of periostin in the diagnosis of asthma through systematic evaluation and meta-analysis.

Methods

Search strategy

We conducted a systematic literature search of 3 databases, including PubMed, EMBASE and Web of Science for relevant studies published through 31 December 2018. We also traced back the relevant references to find additional literature of interest. The search used the following keywords: “asthma” and “periostin.”

Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) diagnostic test design; (2) clinical studies related to asthma and periostin; (3) the index test for periostin; (4) clear diagnostic criteria for asthma; (5) necessary data to reconstruct a 2×2 table from the study. Exclusion criteria were as follows: (1) repeated publication of the study; (2) failure to get the full text and detailed abstract; (3) the articles of review, editorial, letter and conference abstract; (4) the articles of etiology study, mechanism study and animal study; (5) unable to extract the necessary data.

Data extraction

Two researchers independently screened the literatures and extracted the data. When there were divergent opinions, the third researcher determined whether the literature was included or not. Data extraction included the first author's name, publication year, country of study, study design, study subjects, age, sample size, sample type, diagnostic gold standard, cutoff value of periostin in each study and data needed for reconstructing 2×2 tables including the true positive (TP), the false positive (FP), the false negative (FN) and the true negative (TN). When the article met the inclusion criteria but the relevant diagnostic accuracy data was not provided, we contacted the authors to obtain these data, and excluded the article if no response was received. When multiple pairs of sensitivity and specificity data were included in a literature, the cutoff value with the highest Youden index (sensitivity + specificity – 1) was selected.

Quality assessment

Two researchers independently used the Quality Assessment of Diagnostic Accuracy Studies (Quadas-2) tool to evaluate the quality of the included studies (10). The QUADAS-2 tool consisted mainly of four domains: patient selection, index test, reference standard, flow and timing. Researchers assessed the risk of bias by answering the signaling questions of four domains, and graded it into high risk, low risk and

unclear risk. The clinical applicability assessment of the first three domains was also graded into high risk, low risk and unclear risk. We finally summarized in the form of charts.

Data synthesis and statistical analysis

The sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR) and 95% confidence interval of the original study were able to be estimated by 2×2 tables. Bivariate mixed effects model was used to estimate the sensitivity and specificity of logit transformation. The summary receiver operating curve (SROC) was drawn according to the sensitivity and specificity of each study to estimate the accuracy of diagnostic tests.

The “midas” command in Stata software (version 14.1; Stata Corp, College Station, Tex; metandi and midas) was used for meta-analysis. RevMan software (version 5.3; Cochrane Collaboration, Oxford, United Kingdom) was used to make the Quality Assessment graph of risk of bias and applicability concerns. Meta-DiSc 1.4 software (Unit of Clinical Statistics, Hospital Ramo'ny Cajal, Madrid, Spain) was used to analyze the Spearman correlation coefficient in threshold effect.

Heterogeneity and publication bias

In diagnostic experiments, heterogeneity might be caused by threshold effect or non-threshold effect due to the different cutoff values used in different studies. Therefore, we first evaluated the heterogeneity caused by threshold effect by observing the image characteristics of SROC curves and calculating the Spearman correlation coefficient. If the Spearman correlation coefficient was greater than or equal to 0.6 ($p < 0.05$), there was a threshold effect. Cochran's Q test was used to evaluate the heterogeneity caused by non-threshold effect. The test level was $P = 0.05$, and I^2 was used to measure the heterogeneity. An I^2 value of more than 50% was defined as heterogeneous. $P < 0.05$ showed statistical significance (11). The bivariate box plot was used to assess the distribution characteristics of sensitivity and specificity of each study. Deeks' funnel plot was applied to analyze publication bias. The meta-analysis results were presented by forest plots.

Results

Literature search

A total of 1391 studies were identified from PubMed, EMBASE and Web of Science databases. We removed 802 studies after deduplication. By assessing the titles and abstracts, 680 studies were excluded due to

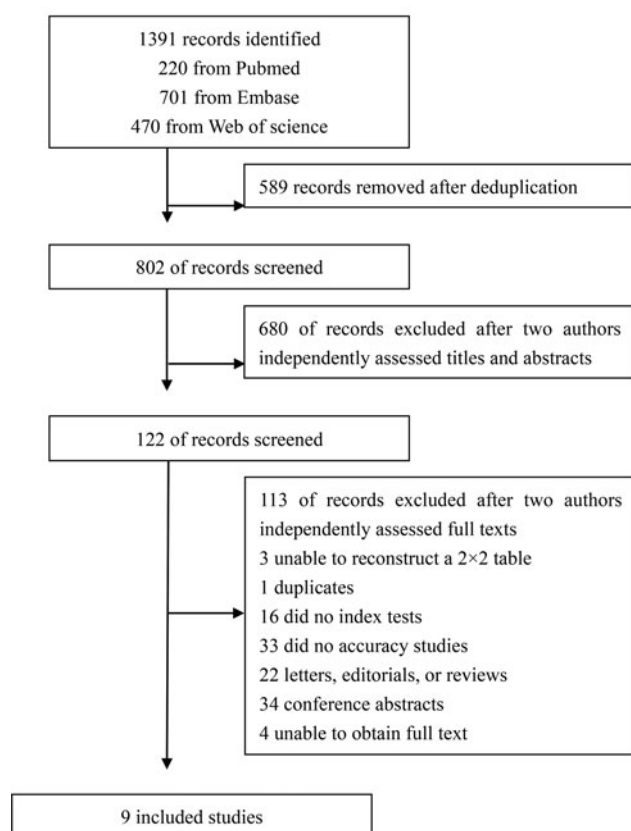


Figure 1. Flowchart for study selection.

repeated publication, irrelevant research contents and topics, basic medical researches and reviews as the article type. We reviewed the full texts of remaining studies and removed 113 articles. The main reasons for excluding were as followed: The full text and necessary data could not be obtained. The article types were reviews, editorials, letters or conference abstract. No index tests and diagnostic accuracy tests were mentioned. Finally, 9 studies were included, and retrospective references were not included in other relevant articles. **Figure 1** shows the study selection and results.

Among the 9 articles included from 2013 to 2018, eight studies were from Asian countries (China, Japan, Korea, India) and one from European country (Poland). All of the articles were case-control studies, two of which were prospective study design. The sample size of each study ranged from 33 to 364, and a total of 1448 subjects were included, including children and adults. The diagnostic gold standard included symptoms, lung function, laboratory results and relevant guidelines for asthma. All cases were diagnosed as asthma. The control groups in all studies were identified as non-asthmatic people, including healthy people and people with

Table 1. Characteristics of included studies.

First author	Year	Country	Sample size	Prospective study	Age	Control	Diagnostic standard	Diagnostic measure	Cutoff value(unit of measurement)	TP	FP	FN	TN
Kanemitsu Y (13)	2013	Japan	290	No	Adult	Healthy	Questionnaire, spirometry, blood tests	Serum	95(ng/ml)	85	1	139	65
Kim M A (26)	2014	Korea	364	No	Adult	Healthy	The Global Initiative for Asthma guideline by clinicians	Serum	54.5(ng/ml)	199	32	78	55
Song J S (27)	2015	Korea	83	No	Children	Healthy	The clinical examination, pulmonary function testing, and methacholine BPT	Serum	90(ng/ml)	15	1	39	28
Emprn V (28)	2016	India	101	Yes	Adult	Healthy	Symptoms, spirometry	Serum	24.56(ng/ml)	69	4	2	26
Gorska K (15)	2016	Poland	33	Yes	Adult	Healthy	Past medical history, symptoms, spirometry, laboratory tests	Bronchial mucosa samples	2+	23	1	0	9
Inoue T (21)	2016	Japan	55	No	Children	Children without asthma	The International Study of Asthma and Allergies in Childhood (ISAAC)questionnaire	Serum	117(ng/ml)	21	11	7	16
Li Y (29)	2017	China	115	No	Children	Healthy	Guidelines for the diagnosis and treatment of bronchial asthma in children (China)	Serum	80.89(ng/ml)	19	4	46	46
Lee J H (14)	2018	Korea	136	No	Adult	Normal	Symptoms	Serum	89.5(ng/ml)	34	10	19	73
Wang J (30)	2018	China	271	No	Adult	COPD	GINA 2015(Global strategy for asthma management and prevention)	Plasma	90.45(ng/ml)	54	30	70	117

COPD chronic obstructive pulmonary disease, GINA global strategy for asthma management and prevention, FN false negative, FP false positive, TN true negative, TP true positive.

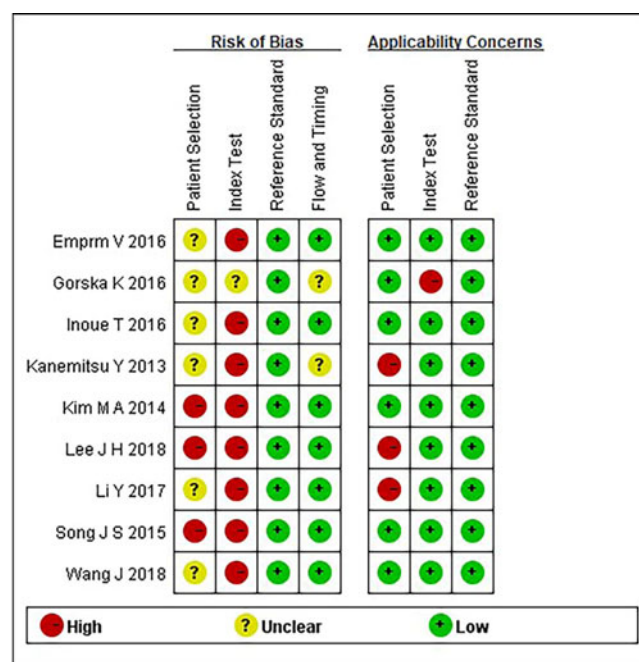


Figure 2. Quality assessment using QUADAS-2 tool for included studies.

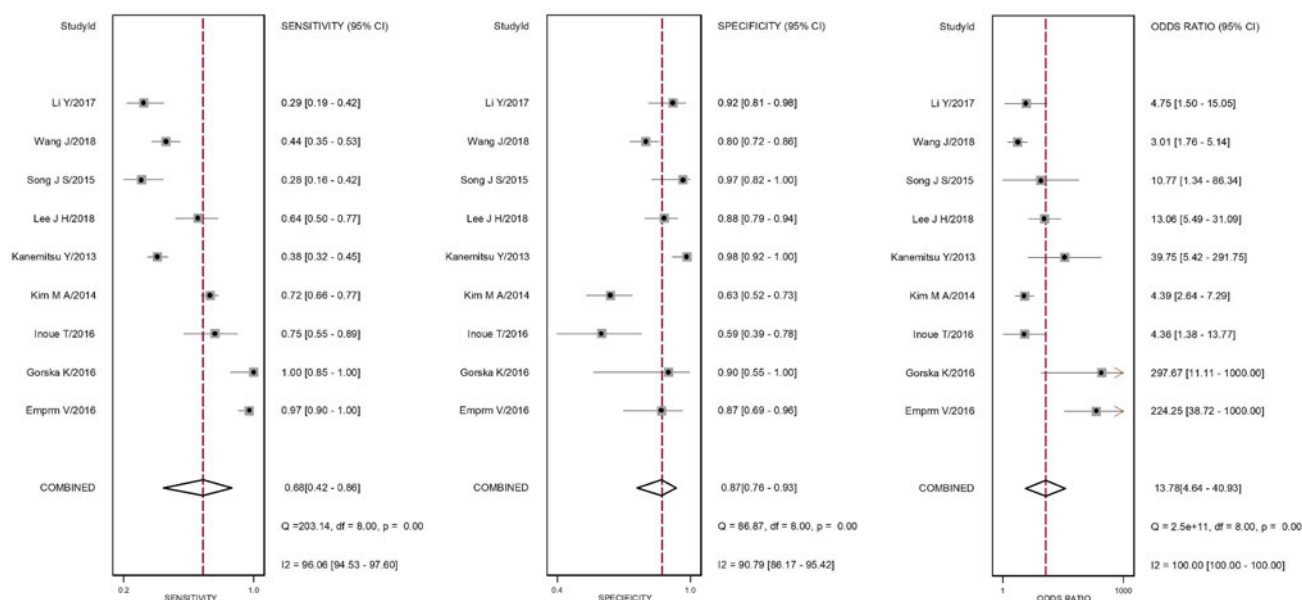


Figure 3. Forest plot of the pooled sensitivity, specificity and pooled diagnostic odds ratio of periostin for included studies.

chronic obstructive pulmonary disease (COPD). Sample types included serum, plasma and bronchial mucosa. Serum and plasma sample units were expressed in ng/ml, and the cutoff values of the studies included were different. The data of 2×2 tables were extracted, including TP, FP, FN and TN. Table 1 shows the basic characteristics of the study.

Quality evaluation

The quality of the included studies was evaluated using the Quadas-2 tool. In terms of the risk of bias,

each study had at least one, with high bias risk mainly occurring in the patient selection and index test. The patient selection resulted in a high risk of bias, mainly due to the fact that all included studies did not avoid case-control studies and did not include subjects with unclear asthma diagnosis. The high bias risk in the index test was mainly due to the fact that all the included studies did not comply with the blind method and the threshold used was not determined before the evaluation. The risk of bias in the reference standard and flow and timing was low. In terms of

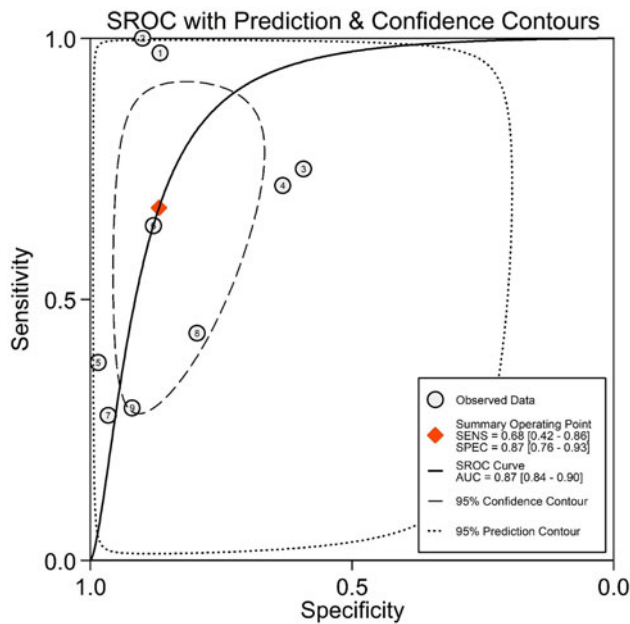


Figure 4. The summary receiver operating curve of periostin in the diagnosis of asthma for included studies: 1: study by Emprn V et al; 2: study by Gorska K et al; 3: study by Inoue T et al; 4: study by Kim M A et al; 5: study by Kanemitsu Y et al; 6: study by Lee J H et al; 7: study by Song J S et al; 8: study by Wang J et al; 9: study by Li Y et al.

the applicability concerns, five of the studies included met all. Figure 2 summarizes the risk of bias and applicability concerns.

Diagnostic accuracy

The combined estimates of sensitivity, specificity, and DOR for the detection of asthma 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) (Figure 3). The under the summary receiver operating curve (AUSROC) was 0.87 (95% CI, 0.84–0.90) (Figure 4).

The Fagan's nomogram plot analysis (Figure 5) showed that with a fixed pretest probability of 20% and a combined PLR of 5, the post-test probability increased to 56%. Conversely, when the NLR was 0.37, the post-test probability was reduced to 9%.

Regression analysis

For heterogeneity analysis, the Spearman correlation coefficient was 0.650 ($p = 0.058$). $P > 0.05$ showed no statistical significance which indicated that the heterogeneity might not be due to the threshold effect. Cochran's Q test showed that the overall I^2 was 100% (95% CI 100.00–100.00) using the bivariate mixed effects model, and heterogeneity might be caused by non-threshold effects. To determine the source of heterogeneity, we performed a univariate regression analysis of the country, study design, age, control group,

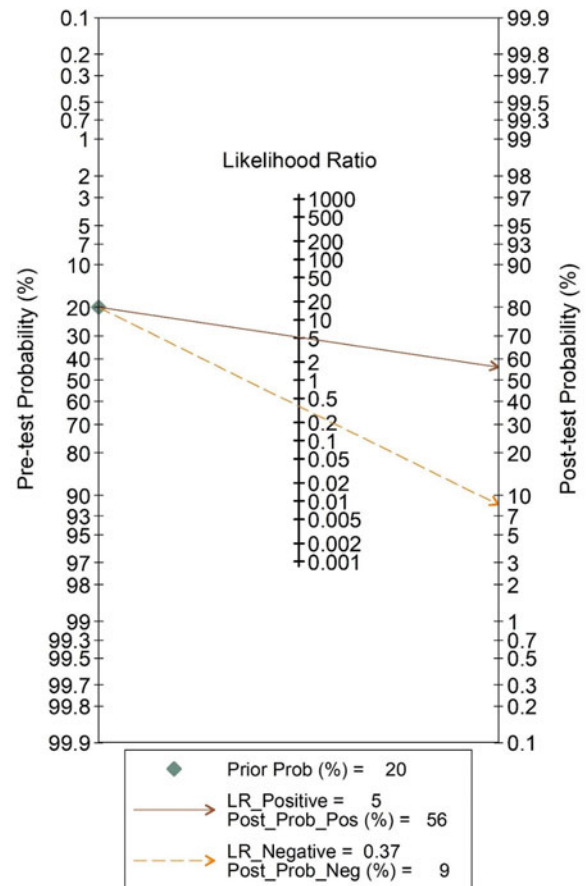


Figure 5. Fagan's nomogram plot analysis for evaluating clinical application value.

and sample type, using Chinese, prospective study design, adult, healthy subjects, and serum samples as controls. From the results, only the study design factors were statistically significant for sensitivity ($P < 0.001$), indicating statistically significant differences in the sensitivity results obtained from prospective and retrospective study designs. For the specificity, the analysis of the above factors did not yield significant results (Figure 6).

In the bivariate box plot analysis (Figure 7), the study by Kanemitsu et al. fell outside the bivariate box plot, indicating that this study might be heterogeneous compared to other studies.

Publication bias

Positive results were more likely to be published than negative results, there might be differences between published and unpublished studies. We used Deeks funnel plot (Figure 8) to assess whether the study had publication bias. First, judging from the graph, the funnel plot was roughly symmetrical, and the asymmetric test result p values shown in the Deeks funnel plot was 0.17 ($p > 0.05$). Therefore, no publication bias was found in this meta-analysis.

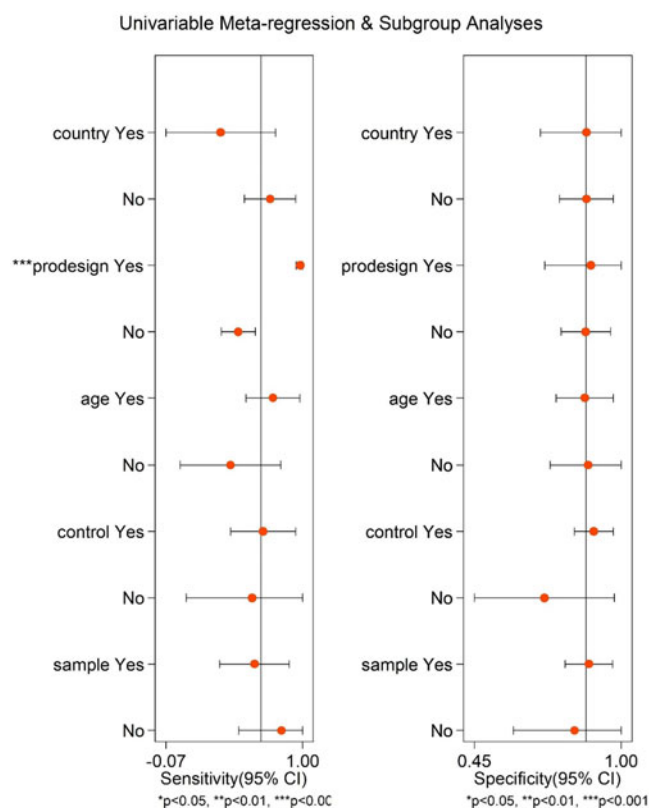


Figure 6. The univariate regression analysis results of periostin in the diagnosis of asthma.

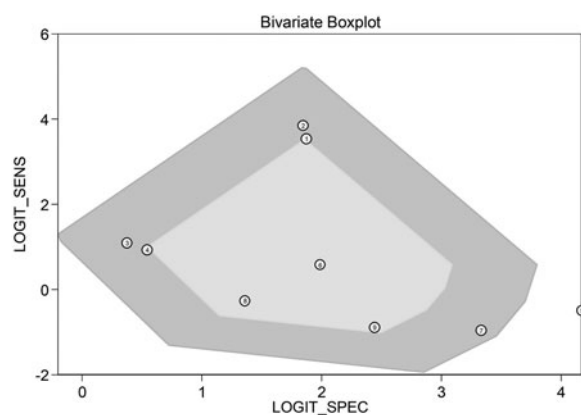


Figure 7. The bivariate boxplot for detecting studies that fall outside: 1: study by Emprn V et al; 2: study by Gorska K et al; 3: study by Inoue T et al; 4: study by Kim M A et al; 5: study by Kanemitsu Y et al; 6: study by Lee J H et al; 7: study by Song J S et al; 8: study by Wang J et al; 9: study by Li Y et al.

Discussion

In view of the uncertain value of periostin in the diagnosis of asthma, we would like to summarize the role of periostin in the diagnosis of asthma through systematic review and meta-analysis. In a recent meta-analysis of the diagnostic accuracy of eosinophilia in asthmatic airways (12), 2919 articles were systematically reviewed. Nine biomarkers were studied to

diagnose asthma. It was found that FeNO, blood eosinophils and serum total IgE were of moderate accuracy in the diagnosis of asthma. Serum periostin was included in only two studies with different diagnostic values. We included nine diagnostic accuracy studies and 1448 subjects. The results showed that periostin was of moderate diagnostic value for asthma. Among the nine studies included, Kanemitsu Y et al. (13) studied asthma patients treated with long-term ICS. Lee J H et al. (14) studied occupational asthma patients caused by Toluene diisocyanate (TDI). The study we included by Gorska K et al. (15) compared the expression of periostin in five sample types. The positive standard of periostin expression in bronchial biopsy samples was not clear. Three researchers consulted and decided to choose 2+ as the cutoff value finally. The sample size of studies to reconstruct 2×2 tables was relatively small. Considering the special type of sample selected and meeting the inclusion criteria, the final decision was to include this study. We excluded two articles which had given some data of ROC curve in the abstract part. However, both articles were conference abstracts, and we could not reconstruct 2×2 tables. After repeated searches, we failed to access full text and the authors were unable to be contacted. So the two studies were eventually excluded. In the process of literature search, we

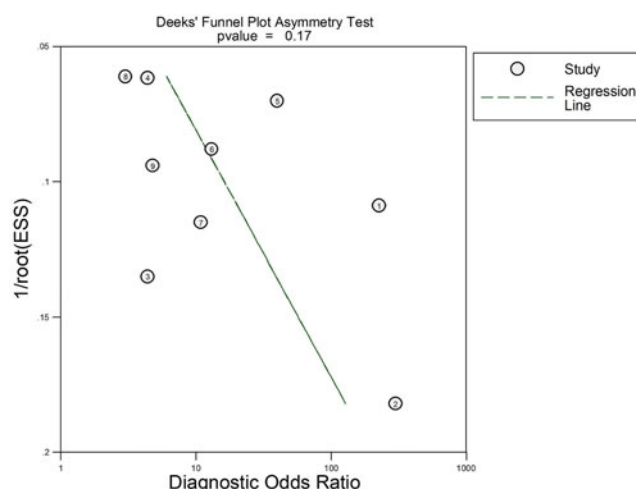


Figure 8. Deeks; funnel plot for detecting publication bias: 1: study by Emprn V et al; 2: study by Gorska K et al; 3: study by Inoue T et al; 4: study by Kim M A et al; 5: study by Kanemitsu Y et al; 6: study by Lee J H et al; 7: study by Song J S et al; 8: study by Wang J et al; 9: study by Li Y et al.

excluded 34 conference abstracts. Such unpublished articles might cause some publication bias. Although Deeks funnel plot showed that this meta-analysis did not produce publication bias, we could not completely exclude the impact of unpublished articles.

Regarding heterogeneity analysis, for the influence of non-threshold effect on heterogeneity, univariate regression analysis only showed that the sensitivity results of prospective and retrospective study design were significantly different. However, due to the lack of data, there were still some variables that we had not studied, such as the choice of gold standard, index test and relevant descriptions of the subjects. More clinical data were needed to identify the sources of heterogeneity. The bivariate box plot analysis showed that the study by Kanemitsu Y et al. (13) might be heterogeneous compared to other studies, which possibly because the case group from this study was asthmatic patients treated with long-term ICS. Studies have shown that serum periostin levels in asthmatic patients without hormone therapy were significantly higher than those in asthmatic patients with hormone therapy (16), which suggested that hormone therapy might have an impact on periostin levels.

Recent studies had shown that COPD was associated with Th2-mediated eosinophilic inflammation (17,18). There was no definite conclusion on the use of periostin as a biomarker to distinguish asthma from COPD and asthma and COPD overlap (ACO) (19,20). Therefore, the diagnosis of these three types needed to be further clarified by the clinical results of other examinations. Studies had shown that there was a significant expression of periostin in bronchial

epithelial cells of asthmatic children (6). Other relevant studies showed that periostin was a meaningful biomarker for the diagnosis of childhood asthma (21,22). At present, there were few articles about periostin in the diagnosis of asthma in children and adults, so that we could not compare the significance of the two diagnostic values. There were various methods to detect periostin. Serum samples were the most common, and other samples included plasma, sputum and bronchial mucosa samples. Airway epithelial cells had high expression of periostin (9). Using the airway epithelial brushings, researchers found that the expression level of IL-13-responsive gene POSTN could divide asthmatic patients into high and low Th2 phenotypes (23). Whether the test value of different samples was quite uncertain

This meta-analysis provided the first systematic review of the diagnostic value of periostin in asthma. However, there were still some limitations in our analysis. First, there were a large number of conference abstracts during literature search and impossible to reconstruct 2×2 tables. While the articles with positive results are easier to publish than those with negative results, which might cause the meta-analysis to overestimate the accuracy of the final diagnosis. Second, the final inclusion results showed that eight articles were from Asian countries and only one article was from Europe. Although univariate regression analysis did not show that the national variable had statistical significance in sensitivity and specificity, but we only chose China as the control group, the bias caused by the region could not be ruled out. Third, only two prospective studies were included. No

studies mentioned blind method, which might easily increase the risk of bias in literature quality assessments. Fourth, the number of studies included in this meta-analysis was relatively small, and the sample size of different studies was quite different. Due to the limited information obtained, the heterogeneity caused by non-threshold effect could not be fully identified as the main source. Finally, the subjects of this study included both adults and children. Because the number of articles of periostin diagnosing children with asthma was too small, subgroup analysis could not be carried out separately. More clinical studies are needed to distinguish the diagnostic value of periostin in children and adults.

For the directions of further research, we think that we should focus on the following points. First, the cutoff values of the studies we included were different. Current studies have not yet determined the diagnostic cutoff value of periostin for asthma. It is necessary to determine the cutoff value for future clinical work. Second, the relationship between periostin and the severity of asthma remains unclear. Whether the severity of the disease can be assessed by the level of periostin remains to be explored. Third, serum, plasma, airway epithelial cells, EBC, induced sputum and other samples can be selected for the detection of periostin. The diagnostic value of different samples remained to be determined. Fourth, in the process of data extraction, we found that there were few studies on the differential diagnosis between asthma and other respiratory diseases. Periostin as a biomarker of eosinophilic airway inflammation was associated with a variety of respiratory diseases, such as COPD, asthma, idiopathic pulmonary fibrosis and so on (24,25). More studies were needed to explore the role of periostin in different respiratory diseases. At last, whether periostin combined with other biomarkers, such as FeNO, serum eosinophils and serum total IgE can improve the diagnostic accuracy of asthma has not been proved. It may become a focus in the future for the diagnosis of asthma.

In conclusion, the meta-analysis of data from nine studies, including 1448 subjects, shows that periostin have moderate accuracy in the diagnosis of asthma, which can be used as an assistant diagnostic marker.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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