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Predictive value of peripheral blood eosinophil levels for eosinophilic chronic rhinosinusitis: A Systematic Review and Meta-analysis

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Abstract

Objective: To evaluate the predictive value of peripheral blood eosinophil levels for eosinophilic chronic rhinosinusitis (ECRS).

Methods: Conducted electronic searches in PubMed, Embase, and the Cochrane Library. Data was analyzed using Stata 16.0.

Results: 23 studies fulfilled the inclusion criteria were analyzed. For peripheral blood eosinophil percentage (BEP) in identifying ECRS, the pooled sensitivity was 0.77 (95% CI: 0.69-0.83) and specificity was 0.74 (95% CI: 0.68-0.80), with positive likelihood ratio (PLR) of 2.97 (95% CI: 2.38-3.72) and negative likelihood ratio (NLR) of 0.31 (95% CI: 0.24-0.42). Similarly, for peripheral blood eosinophil count (BEC), the pooled sensitivity was 0.78 (95% CI: 0.73-0.82) and specificity was 0.73 (95% CI: 0.69-0.77), with PLR of 2.93 (95% CI: 2.45-3.50), NLR of 0.30 (95% CI: 0.24-0.37).

Conclusion: There is not sufficient evidence to support peripheral eosinophilia as a good predictor of ECRS.

Keywords: Rhinosinusitis; Nasal polyps; Eosinophilia; Predictive value of tests

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Introduction

Chronic rhinosinusitis (CRS) is a persistent inflammatory disease affecting the nasal cavity and paranasal sinuses for longer than 12 weeks. Traditionally, CRS was classified into two subtypes primarily based on the absence or presence of nasal polyps: CRS without NPs (CRSsNP) and CRS with NPs (CRSwNP).[1] Further, it can be classified as eosinophilic chronic rhinosinusitis (ECRS) and non-ECRS based on the eosinophilic infiltration level in the nasal mucosa or polyps.[2] The latest European Rhinologic Society Guidelines propose a classification method based on the type of associated inflammation (type 2 or non-type 2 inflammation).[3] ECRS is a type 2 inflammatory disease characterized by good steroid responsiveness, worse olfactory dysfunction, and high recurrence rate after surgery. In contrast, non-ECRS responds well to medical or surgical interventions and exhibits the features of lower postoperative recurrence rate.[4-6] Thus, it is important to discriminate the patients' endotypes and formulate a personalized treatment strategy for CRSwNP patients. Therefore, it is necessary to find a simple classification method that is applicable preoperatively.

Recently, examination of peripheral blood eosinophil has been used as a predictor for the identification of ECRS.[7-29] Unfortunately, the results of these studies are not consistent. Some authors showed that examination of peripheral blood eosinophil may be a useful method for the differential diagnosis of ECRS,[7, 9-13, 16, 19, 23-25] whereas others suggested that serum eosinophilia was not a good marker of tissue eosinophilia.[8, 14, 15, 17, 18, 20-22, 26-29] The associations between peripheral blood eosinophils and tissue histopathology are yet to be defined. Therefore, this study aimed to perform a

systematic review and meta-analysis to evaluate the predictive value of peripheral blood eosinophil levels for ECRS.

Methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplemental Material 1).[30] The protocol used in this article has been registered on PROSPERO and the registry number for this study is CRD42023402824.

Search strategy:

A literature search was performed on PubMed, Embase, Cochrane Library up to April 8, 2024 by two independent reviewers. The search terms were: (((((((Chronic rhinosinusitis) OR (nasal polyps)) OR (CRSwNP)) OR (eosinophilic chronic rhinosinusitis)) OR (ECRS)) OR (ECRSwNP)) AND ((((blood eosinophil count) OR (blood eosinophil percentage)) OR (Eosinophil ratio)) OR (blood eosinophilia))) AND ((((((sensitivity) OR (specificity)) OR (area under the curve)) OR (AUC)) OR (ROC curves)) OR (receiver operating characteristic curves)). No restrictions regarding the publication language were applied. Titles and abstracts of each retrieved study were screened to determine records that should be further evaluated for eligibility. Full texts of the eligible studies were retrieved for further assessment. In addition, the reference lists of the relevant articles were also scanned to identify other potentially eligible studies.

Selection criteria:

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The inclusion criteria were follows: (1) studies that evaluated the predictive value of peripheral blood eosinophils for the diagnosis of ECRS; (2) studies reported complete data on the predictive value of blood eosinophil examination or the number of true-positive, false-positive, true-negative, and false-negative could be extracted; (3) the gold standard for diagnosis of ECRS came from histopathological examination. The exclusion criteria were as follows: (1) case reports, reviews, comments, thesis, and conference abstracts, editorials, letters; (2) data could not be fully extracted; (3) Repeated publications (the research with the largest sample size was selected).

Data Extraction:

Two reviewers extracted the following data independently: first author, publication date, nationality, number of patients, diagnostic criteria of ECRS, blood eosinophil related predictors, cut-off values of predictors for the prediction of ECRS. The outcomes of true-positive, true-negative, false-positive, and false-negative were extracted and cross-checked.

Qualitative Assessment:

The risk of bias of each included study was assessed based on the Quality Assessment of Diagnostic Accuracy Studies–2 (QUADAS-2). QUADAS-2 comprises 4 domains: patient selection, index test, reference standard, and flow and timing. Each domain contains a set of signaling questions and is scored high, low, or unclear by two independent reviewers. Review Manager 5.4 was used for the evaluation of methodological quality in this meta-analysis.

Any discrepancies in the process of article selection, data extraction, and quality

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assessment were resolved through discussions or elucidated by a third party.

Statistical Analysis:

Statistical analysis of the data was performed using Meta-Disc 1.4 and Stata 16.0. Q test and I^2 statistic were used to evaluate heterogeneity among the outcomes of included studies. Significant heterogeneity was indicated by $p < 0.05$ in the Q tests and $I^2 > 50\%$. Pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) with 95% CI were calculated for each blood eosinophil predictor. We also developed a symmetric receiver operator characteristic curve and calculated the area under the curve (AUC). Meta-regression, subgroup analyses and sensitivity analysis were performed to explore the sources of heterogeneity. Deek's funnel plot asymmetry test was used to assess publication bias. $P < 0.05$ was considered statistically significant.

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Results

Eligible Studies:

We identified 635 potentially relevant articles after initial electronic searching. One additional article was identified through a review of reference lists of the relevant articles. 50 articles were left for further selection after removal of duplicates and a review of the titles and abstracts. After full-text screening, 3 studies were excluded because the diagnostic criterion of ECRS was not pathological examination, 2 studies was excluded because the research subjects overlapped with another study, 21 studies were excluded because the essential data could not be extracted, 1 study was excluded because it was a conference abstract. Finally, 23 studies fulfilled the inclusion criteria and underwent data extraction. Study selection and screening proceeded based on the strategy outlined in the standard Preferred Reporting Items for Systematic Reviews and Meta-analysis statement. The article selection process is given in Figure 1. The characteristics of the included studies are summarized in Table 1.

Quality Assessment:

Figure 2 shows the results of quality assessment of included studies according to QUADAS-2 criteria. Of the 23 included studies, 1 study fulfilled 6 items, 8 studies fulfilled 5 items; 14 studies met 4 items. Among them, 22 studies were labeled as unclear in the patient selection domain because the author did not report whether the patients were consecutive or randomly selected. 22 studies were classified as high risk in the index test domain because the threshold used was not pre-specified. The reference standard domain of 15 studies were evaluated as unclear risk because authors did not

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report whether reference standard results were interpreted without knowledge of the results of the index tests.

Predictive value of peripheral blood eosinophils for ECRS:

Of the 23 included articles, 15 reported the predictive value of peripheral blood eosinophil percentage (BEP) for identification of ECRS. Spearman correlation coefficient of BEP was 0.35 (P = 0.20) suggesting that there was no threshold effect. The pooled sensitivity and specificity were 0.77 (95% CI: 0.69-0.83), and 0.74 (95% CI: 0.68-0.80), respectively (Figure 3A). The overall positive and negative likelihood ratios (PLR and NLR) were 2.97 (95% CI: 2.38-3.72) and 0.31 (95% CI: 0.24-0.42), respectively. The pooled diagnostic odds ratio (DOR) was 9.47 (95% CI: 6.31-14.22). The area under the SROC curve (AUC) was 0.82 (95% CI, 0.78–0.85) (Figure 4A; Supplementary material, Table 2).

Seventeen studies reported the predictive values of peripheral blood eosinophil count (BEC) for ECRS. The Spearman correlation analysis revealed a coefficient of -0.10 for BEC (P = 0.71), indicating the absence of a threshold effect. The following results were obtained: pooled sensitivity, 0.78 (95% CI, 0.73-0.82); pooled specificity, 0.73 (95% CI, 0.69-0.77) (Figure 3B); pooled PLR, 2.93 (95% CI, 2.45-3.50); pooled NLR, 0.30 (95% CI, 0.24-0.37); pooled DOR, 9.74 (95% CI, 6.73-14.08); and the AUC was 0.82 (95% CI, 0.78–0.85) (Figure 4B; Supplementary material, Table 3).

Meta-regression and subgroup analysis:

Due to the high heterogeneity in the included studies, we performed meta-regression including patient number (sample size) and diagnostic criteria of ECRS. The meta-

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regression of BEP (Figure 5A) showed that diagnostic criteria had an influence on the heterogeneity of sensitivity and specificity, and patient number led to the difference of sensitivity. The meta-regression of BEC (Figure 5B) showed that both patient number and diagnostic criteria are likely to be the sources of heterogeneity.

Subgroup analyses were conducted based on the number of patients (≥100 or <100) and the diagnostic criteria of ECRS (proportion of tissue eosinophils to the total number of inflammation cells or tissue eosinophils per high-power field) to explore the effects of various study characteristics on the predictive value of BEP and BEC for ECRS. The results of BEP (Figure 5A) indicated that the subgroup with at least 100 patients exhibited lower sensitivity compared to the subgroup with fewer than 100 patients ($p<0.01$). Additionally, the subgroup using the diagnostic criteria of the proportion of tissue eosinophils to the total number of inflammation cells was less sensitive ($p<0.05$) and specific ($p<0.01$) compared to the subgroup using tissue eosinophils per high-power field. Regarding the results of BEC (Figure 5B), the subgroup with at least 100 patients exhibited lower sensitivity ($p<0.001$) but higher specificity ($p<0.01$), while the subgroup using the diagnostic criteria of the proportion of tissue eosinophils to the total number of inflammation cells had lower sensitivity ($p<0.001$) and specificity ($p<0.001$).

Sensitivity analysis:

We then performed a sensitivity analysis by excluding the included studies one by one. The pooled effect size of BEP (Figure 6A) showed no significant change indicating the findings were relatively robust. The pooled effect size of BEC (Figure 6B) decreased significantly after excluding the study by Li 2024-2 and increased after excluding the

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study by Sivrice 2020, indicating that the findings of BEC are not so robust.

Publication bias analysis:

Publication bias was assessed by Deeks' funnel plot asymmetry test. The results (Figure 7) showed that publication bias was not statistically significant for studies regarding BEP (p=0.17) and BEC (p=0.30).

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Discussion

Principal findings:

Peripheral blood is an easily accessible biological sample capable of reflecting the inflammatory state of the body. Some authors recently attempted to examine BEP and BEC to evaluate their predictive value for ECRS patients.[7-29] The systematic review and meta-analysis by Kim et al. compared the differences of BEP and BEC between ECRS and non-ECRS. The results showed that both BEP and BEC were significantly higher in ECRS subgroup than those in non-ECRS subgroup, suggesting blood eosinophil parameter may be used as a simple indicator for subclassification of ECRS and non-ECRS. However, they did not analyze the predictive ability of BEP and BEC for ECRS.[31] In the present study, we conducted a systematic review and meta-analysis of the included 23 clinical studies to evaluate the predictive efficiency of BEP and BEC for the identification of ECRS. The results showed that the pooled sensitivity, specificity, PLR, NLR, and DOR of BEP was 0.77, 0.74, 2.97, 0.31, and 9.47 respectively. BEC exhibited similar value for the identification of ECRS with a pooled sensitivity of 0.78, pooled specificity of 0.73, pooled PLR of 2.93, pooled NLR 0.30, and DOR of 9.74.

Clinical implications:

ROC curve analysis has been widely used to evaluate diagnostic predictors in many fields. The predictive efficiency of a predictor was evaluated by the area under the ROC curve (AUC).[32] An AUC greater than 0.9 indicates high accuracy, while AUCs of 0.7-0.9 and 0.5-0.7 is considered to have moderate and low accuracy, respectively.[33] The results of this study showed that the AUC of BEP and BEC was 0.82, indicating

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moderate diagnostic accuracy for ECRS. In clinical practice, it is important to know how a particular test result predicts the risk of abnormality. The likelihood ratio is a comprehensive index calculated by pooling sensitivity and specificity. It can be used to calculate the probability of abnormality and thus might be more helpful than sensitivity and specificity. According to literature reports, PLR greater than 10 and NLR less than 0.1 suggests excellent accuracy, and PLR greater than 5 and NLR less than 0.2 indicates strong predictive power.[34] The results of this study showed that the PLR of BEP and BEC are 2.97 and 2.93, while the NLR is 0.31 and 0.30 indicating neither BEP nor BEC exhibited sufficient predictive value for ECRS.

Limitations:

This study is limited by several factors. Firstly, studies included in this meta-analysis have certain degree of risk of bias. For instance, the cut-off values of BEP and BEC for diagnosis of ECRS were not preset, but the optimal cut-off value determined based on the ROC curve, which might improve their diagnostic value. Secondly, moderate heterogeneity was found among the included studies. We used meta-regression and subgroup analysis to explore the heterogeneity of data. The results of meta-regression and subgroup analysis indicated that sample size and diagnostic criteria of ECRS can explain the heterogeneity of included studies. However, in the included studies in the present study, different histological criteria were applied to define ECRS, including 16 criteria for the percentage of eosinophils/inflammatory cells (> 10%, > 27%, > 50%), 7 criteria for absolute eosinophil count (> 5, > 10, > 55 eosinophils per HPF). Thirdly, vast majority of included studies were performed in the Chinese

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population. Given the difference in the prevalence of TH2 inflammation and eosinophilic disease between eastern and western countries,[35-38] the results of this meta-analysis may not be applicable to other populations.

Conclusion

In conclusion, this meta-analysis indicates that there is not convincing evidence to support peripheral eosinophilia as a good predictor of ECRS. Given the aforementioned limitations, the conclusion of this meta-analysis should be interpreted with caution.

Summary:

- The results of previous systematic reviews or meta-analyses showed that both peripheral blood eosinophil percentage (BEP) and peripheral blood eosinophil count (BEC) were significantly higher in ECRS patients than those in non-ECRS patients.
- Examination of peripheral blood eosinophil has been used as a predictor for the identification of ECRS.
- This systematic review and meta-analysis has evaluated the predictive value of peripheral blood eosinophil levels for the identification of ECRS.
- 23 studies fulfilled the inclusion criteria were included in this meta-analysis.
- The result of this meta-analysis suggests that there is not sufficient evidence to support peripheral eosinophilia as a good predictor of ECRS.

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Table 1. Characteristics of the Studies included for the Meta-analysis

Author (year)	Country	No. of patients	Criteria of ECRS	Blood eosinophil related predictors	Cut-off value of predictors for the diagnosis of ECRS
Chen 2021	China	77	Tissue eosinophils > 10%	BEP, BEC	BEP: 2.8%, BEC: 0.2085×10^9/L
Du 2020	China	119	Tissue eosinophils > 10%	BEP, BEC	BEP: 2.35%, BEC: 0.18×10^9/L
Han 2022	China	88	Tissue eosinophils > 10/HPF	BEP, BEC	BEP: 3.25%, BEC: 0.175×10^9/L
Ho 2018	Australia	245	Tissue eosinophils > 10/HPF	BEP, BEC	BEP: 4.265%, BEC: 0.235×10^9/L
Hu 2012	China	190	Tissue eosinophils > 10%	BEP, BEC	BEP: 3.05%; BEC: 0.215×10^9/L
Li 2024	China	81	Tissue eosinophils > 10%	BEP	BEP: 5.25%
Li 2024-2	China	1352	Tissue eosinophils > 55/HPF	BEC	BEC: 0.205×10^9/L
Li 2019	China	89	Tissue eosinophils > 27%	BEP, BEC	BEP: 1.9%, BEC: 0.12×10^9/L
Liu 2019	China	48	Tissue eosinophils > 10%	BEP	BEP: 3.40%
Lv 2020	China	70	Tissue eosinophils > 10%	BEP, BEC	BEP: 3.2%; BEC: 0.2×10^9/L
Ma 2023	China	408	Tissue eosinophils > 10%	BEP	BEP: 4%
Sivrice 2020	Turkey	299	Tissue eosinophils > 50%	BEC	BEC: 0.25×10^9/L
Tang 2023	China	139	Tissue eosinophils > 10/HPF	BEP	BEP: 3.45%
Wu 2024	China	116	Tissue eosinophils > 10/HPF	BEC	BEC: 0.265×10^9/L
Xu 2020	China	99	Tissue eosinophils > 10%	BEP	BEP: 3.95%
Zhang 2022-1	China	149	Tissue eosinophils > 10%	BEP	BEP: 3.0%
Zhang 2022-2	China	91	Tissue eosinophils > 10%	BEP, BEC	BEP: 3.950%; BEC: 0.275×10^9/L
Zhong 2021	China	65	Tissue eosinophils > 10%	BEC	BEC: 0.39×10^9/L
Zhou 2021	China	127	Tissue eosinophils > 10%	BEC	BEC: 0.195×10^9/L
Zhou 2023	China	37	Tissue eosinophils > 10/HPF	BEC	BEC: 0.28×10^9/L
Zhu 2020	China	82	Tissue eosinophils > 10%	BEC	NR
Zhu 2023	China	431	Tissue eosinophils > 10%	BEC	BEC: 0.215×10^9/L

Zuo 2014	China	105	Tissue eosinophils > 5/HPF	BEP, BEC	BEP: 2.05%, BEC: 0.16×10^9/L

ECRS indicates eosinophilic chronic rhinosinusitis; BEP, blood eosinophil percentage; BEC, blood eosinophil count; HPF, high power field; NR, not report

Figure 1

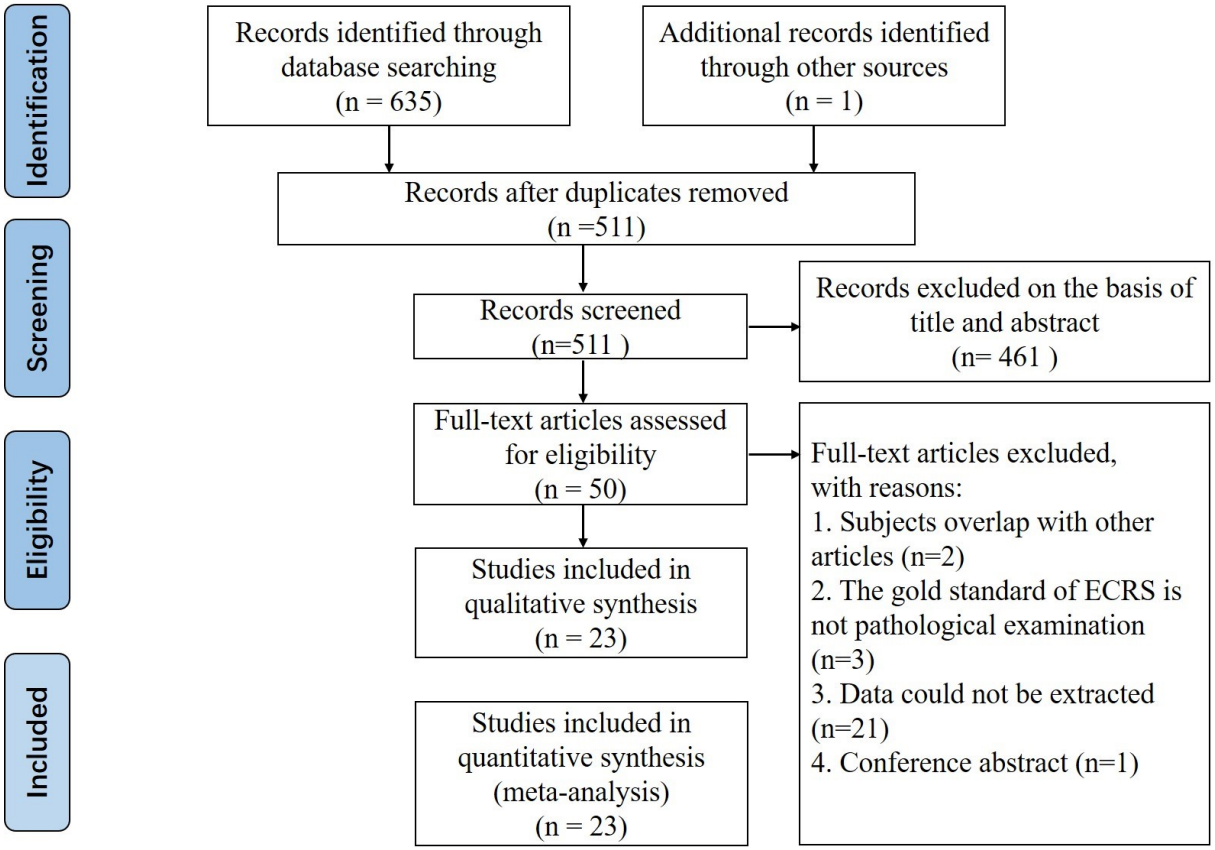

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Figure 2

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Figure 3

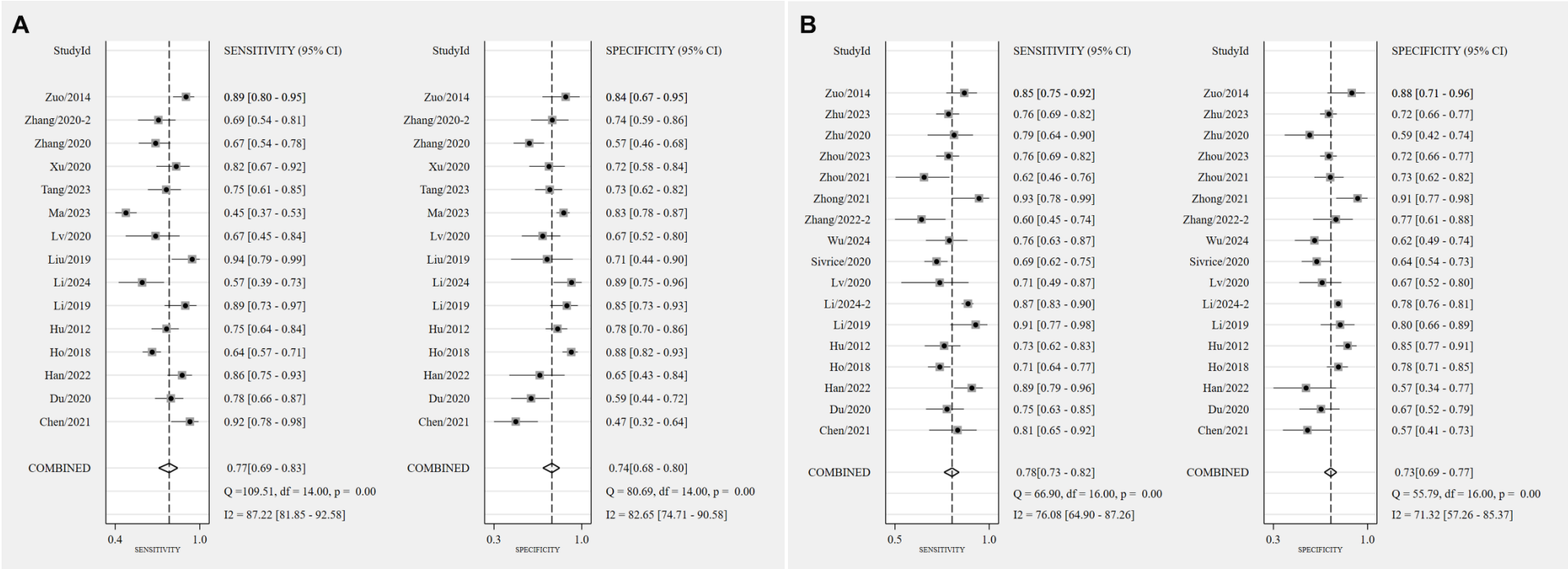

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Figure 4

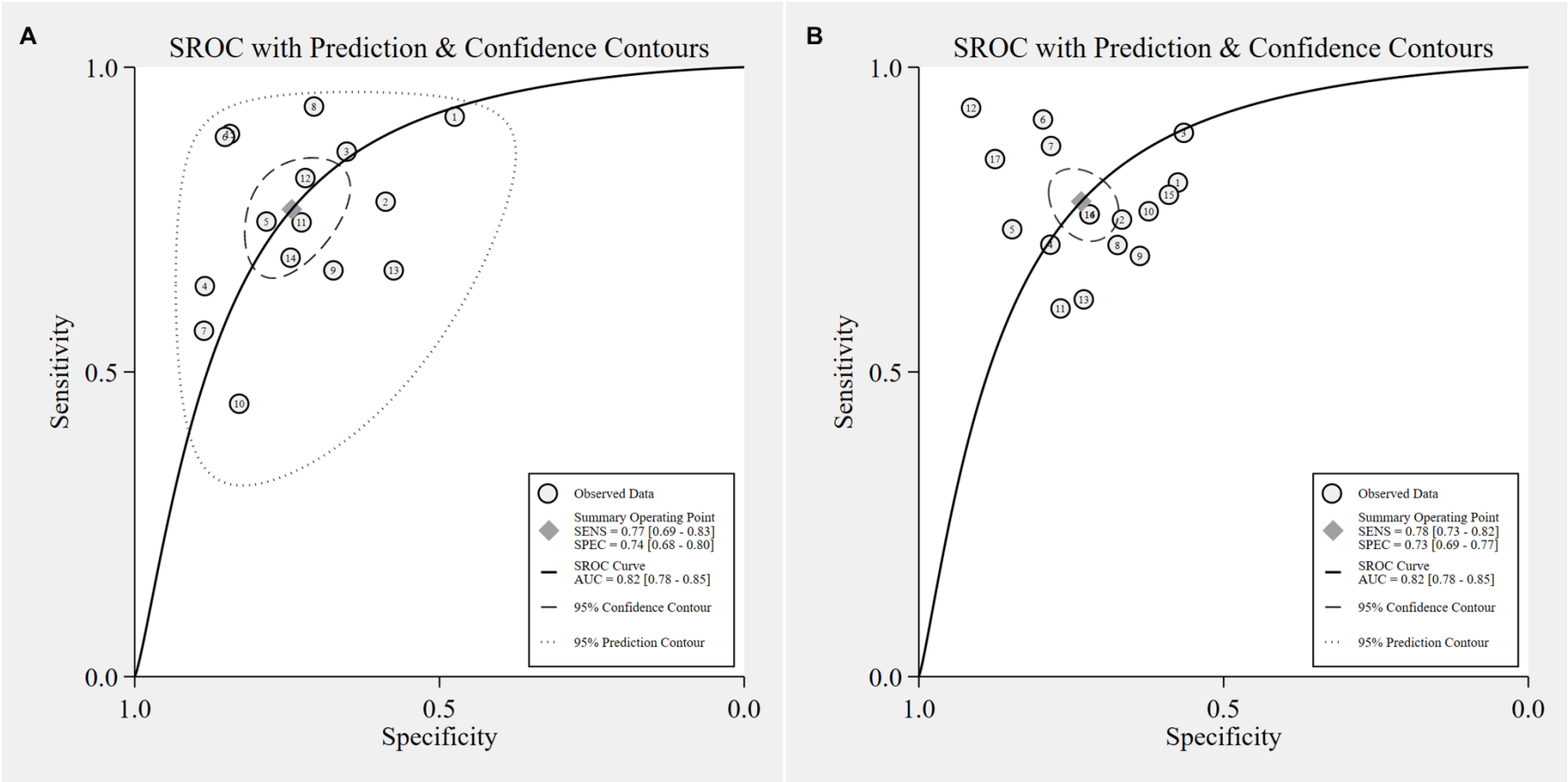

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Figure 5

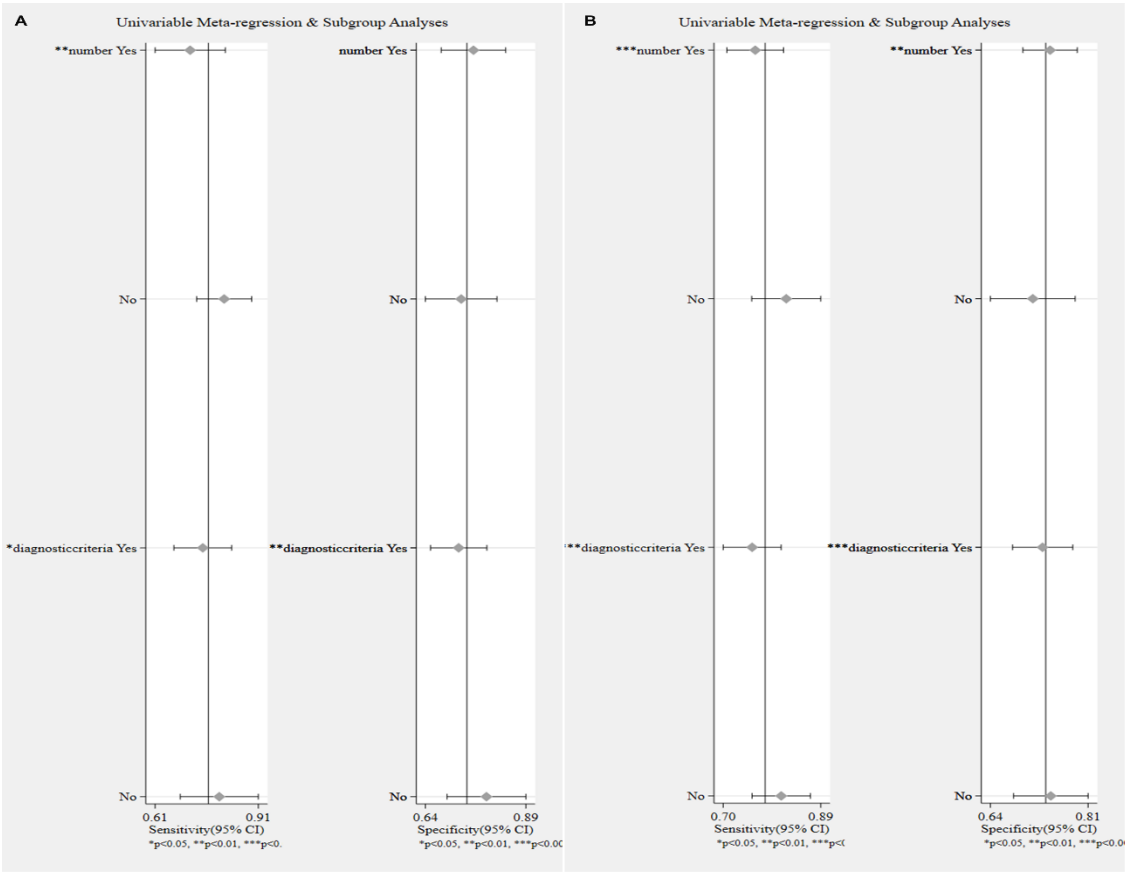

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Figure 6

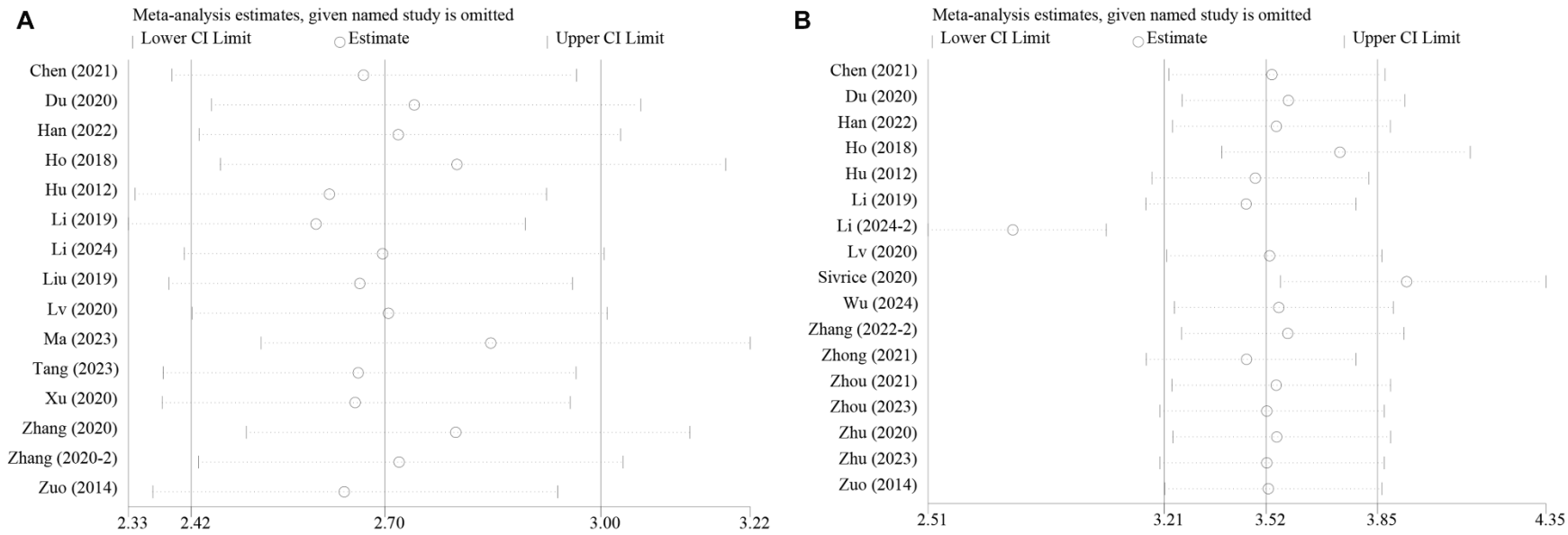

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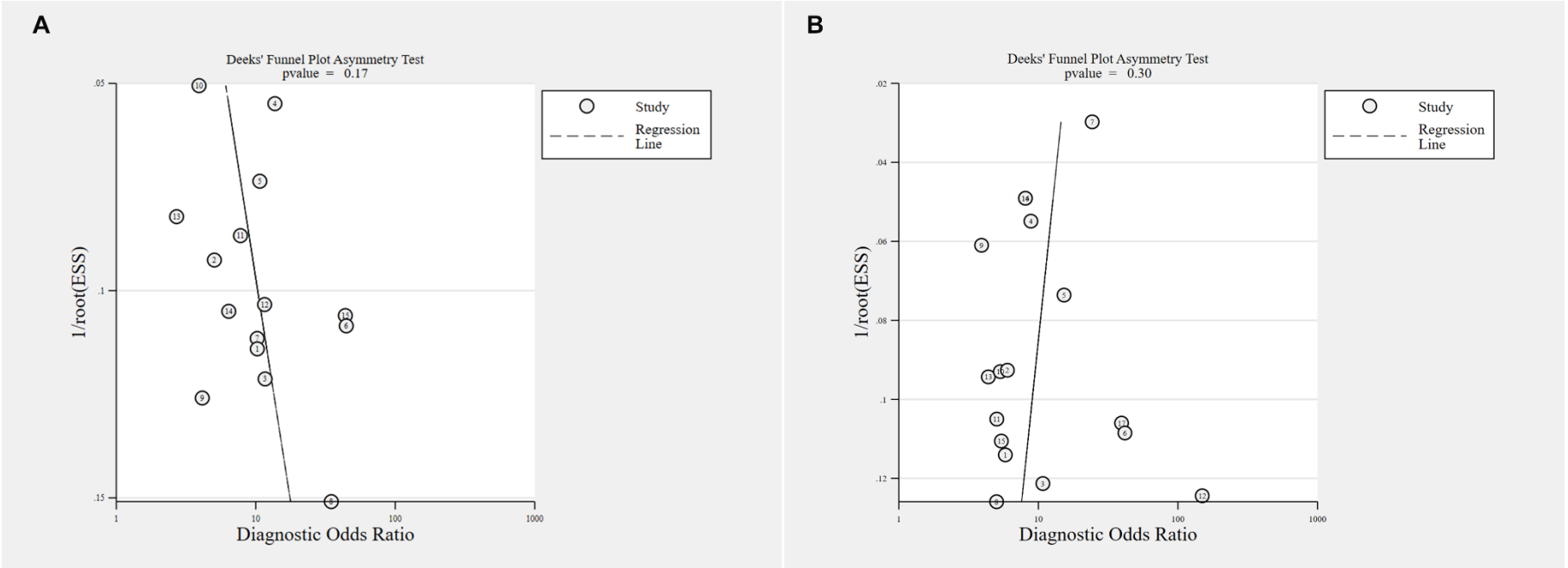
Figure 7



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