

High tissue eosinophilia as a marker to predict recurrence for eosinophilic chronic rhinosinusitis: a systematic review and meta-analysis

Tobial McHugh, MD¹, Kornkiat Snidvongs, MD, PhD², Michael Xie, BSc¹, Sarfaraz Banglawala, MD¹ and Doron Sommer, MD¹

Background: Patients with eosinophilic chronic rhinosinusitis (ECRS) have been shown to have greater disease severity and poorer treatment outcomes after sinus surgery. Although the inflammatory pattern of ECRS is essential to diagnosing this subtype, there is currently no consensus for diagnosis. Our aim in this study was to determine whether high tissue eosinophilia (HTE), measured as eosinophils per high-power field (eos/HPF), could be used to define ECRS based on likelihood of recurrence.

Methods: Embase, Medline, and PubMed databases were searched for studies that reported HTE and recurrence in ECRS patients after surgical treatment. We used a random-effects bivariate meta-analysis to calculate summary sensitivity, specificity, and diagnostic odds ratios (DORs) for detecting ECRS at different HTE cut-off scores using risk of recurrence as the primary outcome.

Results: We identified 11 articles ($n = 3183$) that reported HTE associated with recurrence. A cut-off value of >55 eos/HPF showed the highest sensitivity (0.87; 95% confidence interval [CI], 0.82–0.91), specificity (0.97; 95% CI, 0.93–0.99), and DOR (232.7; 95% CI, 91.0–595.1).

Meta-regression analysis performed showed that the Quality Assessment of Diagnostic Accuracy Studies score ($p = 0.1287$), geographic location ($p = 0.3745$), follow-up time ($p = 0.2879$), and study design ($p = 0.1865$) did not affect the test accuracy.

Conclusion: Our findings suggest that using eos/HPF has good diagnostic accuracy and may be a useful tool for identifying ECRS patients. Based on the results of our meta-analysis, we recommend a cut-off value of >55 eos/HPF for predicting the likelihood of recurrence of ECRS. © 2018 ARS-AAOA, LLC.

Key Words:

chronic rhinosinusitis; eosinophilia rhinitis and nasal polyposis; paranasal sinus disease; disease severity; recurrence; endoscopic sinus surgery

How to Cite this Article:

McHugh T, Snidvongs K, Xie M, Banglawala S, Sommer D. High tissue eosinophilia as a marker to predict recurrence for eosinophilic chronic rhinosinusitis: a systematic review and meta-analysis. *Int Forum Allergy Rhinol*. 2018;00:1–9.

Current classifications divide chronic rhinosinusitis (CRS) into 3 groups: CRS with nasal polyps (CRSwNP); CRS without nasal polyps (CRSSNP); and allergic fungal sinusitis (AFS).^{1–3} Recently, CRS has also

been classified based on underlying inflammatory process into 2 groups: eosinophilic CRS (ECRS) and non-eosinophilic CRS (NECRS).³ Typical features associated with ECRS compared with NECRS^{4–6} are presented in Table 1. ECRS patients represent a unique subtype, as they appear to be more resistant to current medical and surgical interventions.⁷ There is currently a substantial amount of evidence associating ECRS patients with a greater tendency for recurrence of nasal polyps after endoscopic sinus surgery (ESS).^{8–12} Recurrence of nasal polyps poses a significant challenge for otolaryngologists, with long-term recurrence rates ranging from 15% to as high as 50%.^{12–15} Multiple factors, such as comorbid asthma, aspirin sensitivity, allergic rhinitis, peripheral eosinophilia, and adhesion molecule expression, have been associated with polyp recurrence.^{8,10–12,16–20} Among these factors, high tissue eosinophilia (HTE) appears to be the most significant predictor of polyp recurrence.^{11,21} Several publications have

¹Department of Surgery, Division of Otolaryngology, Head and Neck Surgery, McMaster University, Hamilton, ON, Canada; ²Division of Otolaryngology, Head and Neck Surgery, Chulalongkorn University, Bangkok, Thailand

Correspondence to: Tobial McHugh, MD, Department of Surgery, Division of Otolaryngology, Head and Neck Surgery, McMaster University, 3V1 Clinic, 1200 Main Street West, Hamilton, ON L8N 3Z5, Canada; e-mail: tobial.mchugh@medportal.ca

Potential conflicts of interest: K.S.: Merck Sharp Dohme, Glaxo-Smith-Kline (GSK), and Meda (speaker's bureaus); D.S.: GSK (participation in clinical trials).

Received: 24 January 2018; Revised: 15 June 2018; Accepted: 9 July 2018

DOI: 10.1002/alr.22194

View this article online at wileyonlinelibrary.com.

TABLE 1. Comparison of ECRS and NECRS characteristic features*

	ECRS	NECRS
Characteristic symptoms	Reduction/loss of smell in early stages	(Usual)
Endonasal findings	Bilateral polyps, high viscous secretion	Mucopurulent discharge, nasal polyp in middle meatus
CT findings	Bilateral, diffuse inflammation in all sinuses, no demonstrable OMC obstruction, osteoneogenesis ⁵	Demonstrable OMC obstruction ⁶
Blood examination	Eosinophilia	—
Coexistence of asthma	Frequent	Less frequent
Macrolide therapy	Not effective	Effective
Recurrent rate of nasal polyps	Very high	Low
Systemic steroid for recurrence	High efficacy	Unclear
Histology of nasal polyps	Eosinophilia, lymphocyte infiltration, basement membrane thickening (remodeling)	Lymphocyte infiltration, increased nasal glands

*Adapted from Ishitoya et al.⁷

CT = computed tomography; ECRS = eosinophilic chronic rhinosinusitis; NECRS = non-eosinophilic chronic rhinosinusitis; OMC = ostiomeatal complex.

proposed various threshold values for HTE, varying from >5 eos/HPF to >120 eos/HPF.^{10,11,16,18} Accordingly, debate remains regarding a clear definition and diagnostic criteria for ECRS that would aid in prognostication and treatment.

The purposes of this systematic review were to determine whether tissue eosinophilia is an appropriate marker for identifying patients who are at higher risk of recurrent disease. A secondary aim was to perform a meta-analysis and propose a value for HTE that is most predictive of recurrence.

Materials and methods

Literature search strategy and selection criteria

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,²² we undertook a systematic review and meta-analysis to determine the diagnostic accuracy of tissue eosinophilia (measured as absolute number of eosinophils per high-power field [eos/HPF]) for diagnosing ECRS based on likelihood of recurrence. We searched Embase, Medline, and PubMed from 1996 to June 2018 for studies that reported tissue eosinophilia and recurrence of disease in patients with CRS after surgical treatment. The electronic database was searched using keywords including: “sinusitis” OR “chronic rhinosinusitis” OR “rhinosinusitis” OR “polyp*” combined with “eosinophil*” AND “recurrence.” Relevant articles and abstracts were selected and reviewed. Reference lists from these sources and recent review articles were searched for additional publications. Articles were screened and assessed for eligibility independently by 2 review authors (T.M. and M.X.), obtaining

full-text articles to assess for relevance where necessary. We included only selected articles that measured absolute tissue eosinophilia count within the sinus mucosa and polyps of CRS patients. Articles that did not report recurrence were excluded. Study characteristics, recurrence rates, measures, and values of tissue eosinophils used by each study were recorded. Observational and experimental studies were included in our search. Non-English-translated publications were excluded. Where appropriate, authors were contacted to clarify specific details related to their publications (eg, measurements of HPF, specific patient details).^{11,12,23,24} Two attempts were made to contact corresponding authors for those publications that required additional clarification.

Assessment of quality

Methodological quality of identified studies was appraised using the updated Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool.²⁵ This tool assesses the quality of included studies in terms of risk of bias and concerns regarding applicability over 4 domains (patient selection, index test, reference standard, and flow).

Data synthesis and statistical analysis

We constructed 2 × 2 tables for multiple different tissue eosinophilia cut-off scores using risk of recurrence as the primary outcome and computed the sensitivity, specificity, positive and negative likelihood ratios (LRs), and diagnostic odds ratio (DOR). A bivariate meta-analysis at cut-off points between 5 and 120 eos/HPF was performed by calculating the pooled estimates of specificity and sensitivity and their associated 95% confidence intervals (CIs)²⁶ using DerSimonian-Laird weights for the random-effects model. We constructed summary receiver operating characteristic

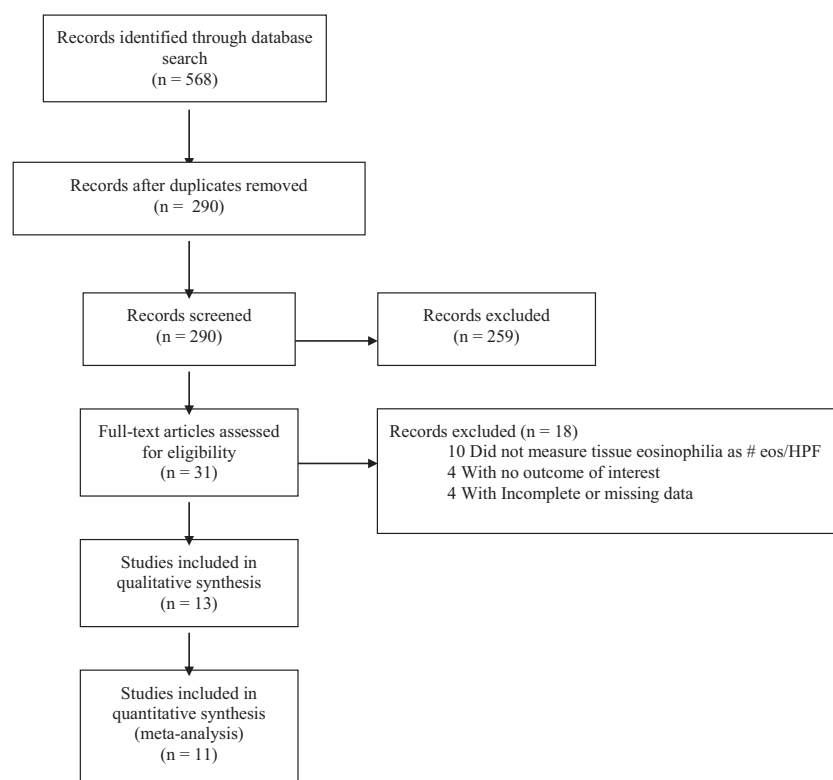


FIGURE 1. Flow diagram of study selection. eos/HPF = number of eosinophils per high-power field.

(SROC) curves²⁶ using a bivariate model to produce a 95% confidence ellipse within the receiver operating characteristic (ROC) curve space.²⁷ We calculated the respective area under the curve (AUC) and Q^* , where sensitivity = specificity on the summary ROC curve, corresponding to the upper leftmost point on the SROC. The diagnostic accuracy of HTE for polyp recurrence is represented by AUC. A model with an AUC of 0.9-1.0 indicates excellent accuracy, 0.8-0.9 indicates very good accuracy, 0.7-0.8 indicates good accuracy, 0.6-0.7 indicates sufficient accuracy, 0.5-0.6 indicates poor accuracy, and <0.5 indicates that the test is not useful.²⁸

We assessed between-study heterogeneity using the I^2 statistic for the pooled DOR.²⁹ We considered an I^2 value of <25% to be low, 50% to be moderate, and >75% to be high. We explored the causes of heterogeneity if there was significant between-study heterogeneity. We identified the studies that were outside of the 95% confidence ellipse by visually inspecting the SROC curve plots. The presence of a threshold effect on the diagnostic accuracy of HTE was evaluated using the Spearman correlation coefficient between the logits of sensitivity and specificity. We also performed meta-regression analyses to identify the effect of potentially confounding variables. The presence of publication bias was tested using funnel plots and the Egger test.³⁰ $p < 0.05$ was considered statistically significant. Descriptive data are presented as percentage and mean $\pm$ standard deviation (SD). All calculations and plot syntheses were performed using commercially available statistical

software (Cumulative Meta-Analysis version 3 and Meta-DiSc version 1.4).

Results

Description of studies

The initial database search revealed 568 potential articles, whereby 290 remained after duplicates were removed. From these, 259 were excluded on the basis of title and abstract review for being irrelevant to our study question, leaving 33 potentially relevant studies. Full articles of potentially eligible studies were reviewed in depth and their references mined. Finally, 11 individual studies met our inclusion criteria for both the qualitative synthesis and quantitative meta-analysis^{8,10,11,14,20,21,24,31-34} Figure 1 shows the study selection process.

Table 2 summarizes the main characteristics and results of the included studies. A total of 3183 patients were included in the meta-analysis. Seven studies were prospective and 4 were retrospective. Geographically, 5 studies included patients from a Western region and the remaining 6 studied an Asian region (China or Japan). A total of 827 patients had recurrent disease, with a mean follow-up time of 31 ± 14.3 months. The average risk of recurrence was 26% and the average time for detecting recurrence after surgical treatment was 23 months. The criteria defining HTE ranged from >5 to >120 eos/HPF. The authors' explanations and their definitions of recurrence are detailed in Table 2.

TABLE 2. Characteristics of the studies included in the meta-analysis

Study	Study design	Country	HTE criteria (eos/HPF)	Author's reason for defining HTE	Biopsy location	Author's definition of recurrence	Mean time to recurrence (months)	Follow-up (months)	Number of patients (ECRS / NECRS)	Recurrent disease (ECRS / NECRS)
Brescia et al (2015)	P	Italy	>10	No specific reason provided	NP	Grade ≥ 1 NP	22.3 $\pm$ 10.7	32.8 $\pm$ 14.7	n = 179 (74 / 105)	n = 24 (16 / 8)
Brescia et al (2016)	P	Italy	>10	No specific reason provided	NP	Grade ≥ 1 NP	19 $\pm$ 10	17 $\pm$ 10	n = 143 (56 / 87)	n = 21 (13 / 8)
Do et al (2016)	P	Australia	>10	Based on Snidvongs et al (2012) ⁵	Ethmoid mucosa	Requirement of long-term oral steroids	NR	>12	n = 110 (61 / 49)	n = 9 (8 / 1)
Grgic et al (2015)	P	Croatia	>20	Highest RR for polyp recurrence (RR, 41%; $p < 0.05$)	NP	Grade ≥ 1 NP	NR	24	n = 30 (22 / 8)	n = 11 (9 / 2)
Ikedo et al (2013)	P	Japan	>100	ROC curve and Cox proportional hazard model showed the minimum p value	NP	Presence of NP middle meatus	28 $\pm$ 12	48	n = 130 (42 / 88)	n = 47 (20 / 22)
Lou et al (2015)	R	China	>55	Youden index: optimal sensitivity, specificity and AUC (0.969; $p < 0.001$).	NP	Recurrent NP, 1 year postsurgery with symptoms > 1 month	NR	34 $\pm$ 5	n = 387 (192 / 195)	n = 214 (187 / 27)
Matsuaki et al (2008)	R	Japan	>120	Highest odds ratio for recurrence (OR, 3.2; $p < 0.001$)	NP or sinus mucosa	Need for revision ESS	NR	60	n = 56 (7 / 49)	n = 9 (6 / 3)
Nakayama et al (2011)	P	Japan	>70	Showed the minimum p value ($p = 0.001$) and highest AUC (0.673)	NP or ethmoid mucosa	Grade ≥ 1 NP	NR	17.5	n = 175 (89 / 86)	n = 40 (31 / 9)
Nakayama et al (2016)	R	Japan	>70	Based on Nakayama et al (2011) ¹¹ and Tokunaga et al (2015) ²³	NP	Lund-Kennedy mucosal edema score ≥ 2	NR	36.9 $\pm$ 10.3	n = 36 (16 / 20)	n = 17 (10 / 11)
Tokunaga et al (2015)	R	Japan	>70	Most significant value for Kaplan-Meier curve recurrence free rate.	NP	Grade ≥ 1 NP	NR	22.6	n = 1716 (672 / 1044)	n = 396 (222 / 174)
Vlaminck et al (2014)	P	Belgium	>5	Based on Soler et al (2009) ¹⁹	Sinus mucosa	Recurrent diseased mucosa with ≥ 3 sinus symptoms ≥ 1 month with systemic steroids	NR	36	n = 221 (128 / 93)	n = 49 (41 / 8)

AUC = area under the curve; ECRS = eosinophilic chronic rhinosinusitis; ESS = endoscopic sinus surgery; HPF = high-power field; HTE = high tissue eosinophilia; NECRS = non-eosinophilic chronic rhinosinusitis; NP = nasal polyps; NR = not reported; NRD = non-recurrent disease; OR = odds ratio; P = prospective; R = retrospective; RD = recurrent disease; ROC = receiver operating characteristic; RR = relative risk.

TABLE 3. QUADAS-2 assessments of the included studies

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Brescia et al (2015)	Low	Unclear	Low	Low	Low	Low	Low
Brescia et al (2016)	Low	Unclear	Low	Low	Low	Low	Low
Do et al (2016)	Low	Low	Low	Unclear	Low	Low	Low
Grgic et al (2015)	Low	High	Unclear	Low	Low	Low	Low
Ikeda et al (2013)	Low	High	Unclear	Low	Low	Low	Low
Lou et al (2015)	High	High	Unclear	Low	Low	Low	Low
Matsuwaki et al (2008)	High	High	Unclear	Low	Low	Low	Low
Nakayama et al (2011)	Low	High	Unclear	Low	Low	Low	Low
Nakayama et al (2016)	High	Low	Low	Low	Low	Low	Low
Tokunaga et al (2015)	High	High	Unclear	Low	Low	Low	Low
Vlaminck et al (2014)	Low	Low	Low	Low	Low	Low	Low

QUADAS = Quality Assessment of Diagnostic Accuracy Studies.

TABLE 4. Pooled estimates of the sensitivity, specificity, positive and negative likelihood ratios, and diagnostic odds ratios of high tissue eosinophilia for diagnosing ECRS, by cut-off score

Cut-off score (eos/HPF)	Number of studies	Number of patients	Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)
>5	1	221	0.84 (0.71-0.92)	0.49 (0.42-0.57)	1.65 (1.36-2.01)	0.33 (0.17-0.63)	5.01 (2.26-11.10)
>10	3	432	0.69 (0.55-0.79)	0.59 (0.54-0.64)	1.68 (1.35-2.09)	0.53 (0.36-0.79)	3.17 (1.73-5.79)
>20	1	30	0.82 (0.51-0.96)	0.32 (0.15-0.54)	1.20 (0.79-1.81)	0.58 (0.14-2.38)	2.08 (0.39-11.12)
>55	1	387	0.87 (0.82-0.91)	0.97 (0.93-0.99)	30.23 (12.73-71.83)	0.13 (0.09-0.19)	232.71 (91.01-595.05)
>70	3	1927	0.67 (0.54-0.79)	0.57 (0.49-0.65)	1.58 (1.22-2.03)	0.57 (0.39-0.84)	2.76 (1.48-5.15)
>100	1	130	0.53 (0.36-0.69)	0.76 (0.66-0.84)	2.20 (1.40-3.53)	0.62 (0.44-0.89)	3.54 (1.60-7.84)
>120	1	56	0.67 (0.30-0.93)	0.98 (0.88-1.00)	31.33 (4.27-229.97)	0.34 (0.14-0.86)	92.00 (8.20-1032.30)

CI = confidence interval; DOR = diagnostic odds ratio; ECRS = eosinophilic chronic rhinosinusitis; eos/HPF = number of eosinophils per high-power field; NLR = negative likelihood ratio; PLR = positive likelihood ratio.

Quality assessment

The findings of the methodological quality assessment for all studies included in our meta-analysis using the QUADAS-2 tool are presented in Table 3. Four domains of risk of bias and 3 domains of applicability were assessed. We attributed a score of 1 point for each “low” value, 0 point for each “high” value, and 0.5 point for each “unclear” value. The maximum score using the QUADAS-2 tool is 7. Using this scoring system, the mean score for all included studies was 81% (5.7 of 7).

Meta-analysis and diagnostic accuracy of HTE

Eleven studies (3183 patients, 837 with recurrence) were included in the analysis and we pooled all studies with the

same cut-off scores (Table 4). The overall pooled sensitivity (95% CI) of using HTE for predicting recurrence was 78% (74%-82%) and the pooled specificity was 66% (64%-69%). The pooled positive LR (95% CI) was 2.8 (1.5-5.1) and negative LR was 0.39 (0.22-0.69). The pooled DOR was 8.6 (2.5-29.0). In general, a cut-off value of >55 eos/HPF showed the highest sensitivity (0.87; 95% CI, 0.82-0.91), specificity (0.97; 95% CI, 0.93-0.99), positive LR (30.2; 95% CI, 12.7-71.8), and DOR (232.7; 95% CI, 91.0-595.1).

Threshold analysis and SROCs

As shown in Figure 2, a positive correlation was noted between sensitivities and 1 – specificities. The Q* value,

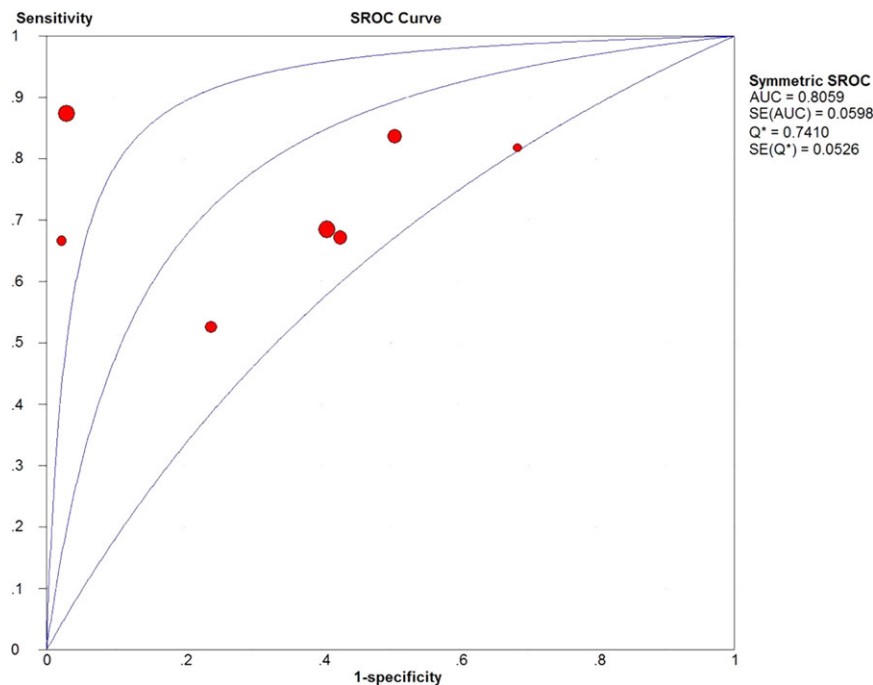


FIGURE 2. Summary receiver operating characteristic (SROC) curve. Each circle represents each cut-off value used in the meta-analyses. The overall size associated with each cut-off value is indicated by the size of the circle. The regression summary receiver operating characteristic curves summarize the overall diagnostic accuracy.

representing the highest common value of sensitivity and specificity, was 0.74 (standard error [SE], 0.0526) and the AUC was 0.81 (SE, 0.0598), indicating moderate diagnostic accuracy. No statistically significant difference was observed when exploring for threshold effect (Spearman correlation coefficient = 0.32; $p = 0.482$).

Investigation of heterogeneity

The χ^2 test was used to evaluate the presence of statistically significant heterogeneity across the studies and the inconsistency index (I^2) was used to quantify the amount of heterogeneity. Statistical heterogeneity and inconsistency were found for sensitivity ($p < 0.001$, $\chi^2 = 32.36$, $I^2 = 81.5\%$), specificity ($p < 0.001$, $\chi^2 = 181.71$, $I^2 = 96.7\%$), positive LR ($p < 0.001$, $\chi^2 = 124.87$, $I^2 = 95.2\%$), negative LR ($p < 0.001$, $\chi^2 = 53.04$, $I^2 = 88.7\%$), and DOR ($p < 0.001$, $\chi^2 = 76.05$, $I^2 = 92.1\%$).

Meta-regression analysis

Because of the interstudy heterogeneity, we performed a meta-regression. We chose to investigate whether the QUADAS-2 score, geographic location, and mean follow-up time, and whether the studies were prospective or retrospective studies were responsible for the heterogeneity noted. The meta-regression analysis we performed showed that QUADAS-2 score ($p = 0.1287$), geographic location ($p = 0.3745$), follow-up time ($p = 0.2879$), and whether the studies were prospective or retrospective studies ($p = 0.1865$) did not affect the test accuracy.

Evaluation of publication bias

Overall, to address the potential publication bias that may be introduced during the meta-analysis, Egger tests and Begg funnel plots were utilized as control. Publication bias was not identified by either Egger testing (intercept = 1.93; 95% CI, -1.38 to $5.25.07$; $t = 1.34$; $df = 8$; $p = 0.2157$) or Begg funnel plots (Fig. 3), which indicates the absence of publication bias in our meta-analysis results.

Discussion

ECRS patients present a challenge for both diagnosis and treatment. A review of the literature shows that tissue eosinophilia counts of >5 or >10 eos/HPF appear to be most commonly used to define tissue eosinophilia. These values were primarily based and referenced to 3 studies. Kountakis et al defined HTE as >5 eos/HPF based on higher postoperative endoscopy scores.¹⁶ Soler et al used a value of >10 eos/HPF based on significantly lower improvements in quality-of-life outcomes on long-term follow-up posttreatment.¹⁸ Snidvongs et al found a cut-off point of >10 eos/HPF related to steroid irrigation responsiveness.³⁵ The tissue eosinophilia values determined by recurrence tended to correlate with these values when limited to a Western demographic. We felt that choosing recurrence would therefore be a suitable outcome marker to use for our analysis.

This is the first systematic review investigating the diagnostic properties of HTE for ECRS at different cut-off scores. In general, our results suggest that HTE may be an

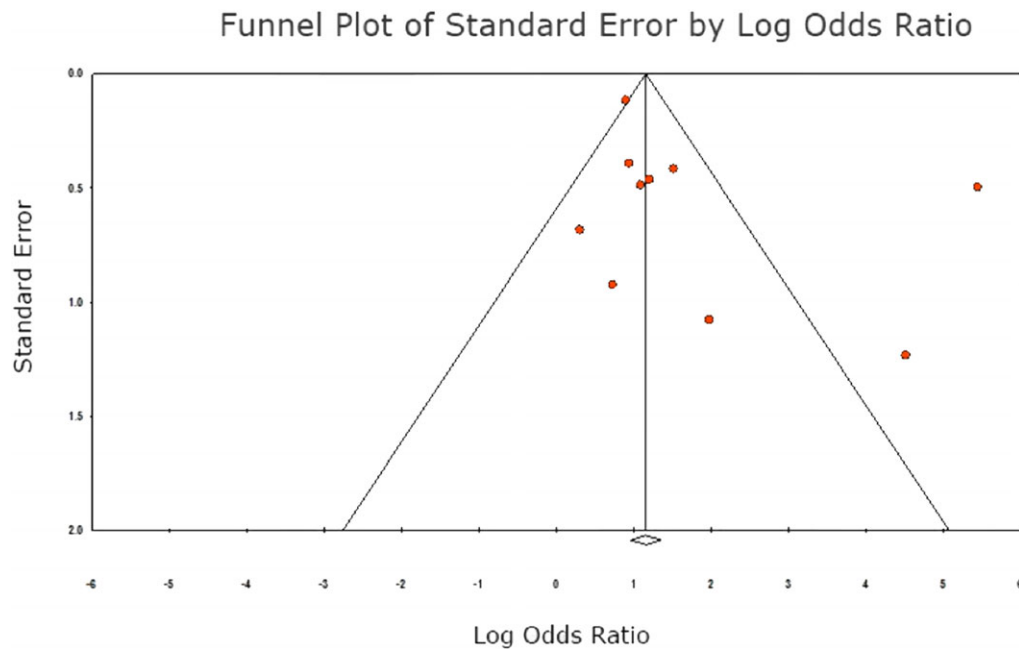


FIGURE 3. Funnel plot of the included studies in the meta-analysis for the assessment of potential publication bias.

acceptable marker for diagnosing ECRS patients based on likelihood of recurrence. The overall diagnostic accuracy of HTE was found to be moderate despite clinical heterogeneity of the included studies, as the area under the SROC curve was 0.81. The pooled sensitivity of HTE for predicting recurrence was 78% and the specificity was 66%. Pooled positive LR was 2.81. With a hypothetical pretest probability of 25%, using HTE as a marker to predict recurrence would raise the posttest probability to 48%. With a negative likelihood ratio of 0.39, using HTE reduces the posttest probability to 11%, thereby supporting that the application of HTE may be helpful in ruling out the risk of recurrence.

The highest overall sensitivity, specificity, and DOR was identified when a cut-off value of >55 eos/HPF was used. We therefore recommend using this value to predict recurrence in ECRS. However, it is important to mention that these data were largely gleaned from an Asian demographic. For Western patients, a cut-off value of >5 eos/HPF yielded the best sensitivity, specificity, and DOR. It is unclear whether this difference is strictly due to environmental exposures and geographic location, or whether race and inherent genetic differences play an underlying role for this variation. For example, would an Asian population living in a Western country express inflammatory patterns similar to people in their regional environment, or would they demonstrate more similar patterns to people from an Asian country? Unfortunately, the way current studies are designed does not allow us to answer this question. Future studies within Western countries will be needed to investigate whether there is a difference in underlying nasal polyp inflammatory patterns based on race. The mean risk of recurrence from all included studies was 26%. This value falls

within the fairly wide range of 15%-50% reported in previous studies.¹²⁻¹⁵ Within our included studies, there was a significant risk of recurrence difference between Western and Asian populations (16.7% vs 28.9%, respectively; $p < 0.0001$). Assuming similar surgical and perioperative practices, given this difference in recurrence and cut-off values, it is plausible that using lower threshold values in an Asian population may narrow the gap between these populations. From the Nakayama et al analysis,¹¹ the authors calculated hazard ratios measuring mucosal eosinophilia and risk of recurrence beginning with >10 eos/HPF and increasing by increments of 10 up to >150 eos/HPF. From their analysis, the value with the highest AUC was >70 eos/HPF and was therefore selected as their cut-off value. Interestingly, the values set at lower thresholds still produced acceptable results that were statistically significant. This only further reinforces a need to specifically address this question.

The overall pooled DOR was 8.6 (95% CI, 2.5-29.0; $p < 0.001$). The DOR is a single indicator of test accuracy.³⁶ However, some cut-off values achieved a DOR as high as 232.7 and 92.0, based primarily on studies by Lou et al¹⁰ and Matsuwaki et al,¹⁴ respectively. The disparity noted in this situation may be attributed to study design, where the values for HTE cut-off scores in those studies were determined *a posteriori*. Moreover, other discrepancies may also be related to various additional factors, such as differences in the nature of the study population, length of follow-up time, extent of surgery and postsurgery treatment regimens, and compliance. Because CRS appears to be a life-long inflammatory condition,³⁷ we can assume that longer follow-up duration would demonstrate a higher overall risk of recurrence. This is supported by the fact that the study

with the highest DOR also had the longest follow-up period (60 months).

Limitations

The methodological quality of the studies varied, and the level of between-study heterogeneity was consistently high. Due to the fact that our meta-analysis revealed marked heterogeneity with regard to sensitivity, specificity, positive LR, negative LR, and DOR, we undertook a meta-regression analysis to explore the possible reasons for this heterogeneity.³⁸ However, none of the variables included in the meta-regression analysis were found to affect the diagnostic accuracy of HTE. The 11 studies included in this review were considered to be of good quality, with an overall QUADAS-2 score of >5. Although the type of study included (prospective or retrospective) was not found to affect the diagnostic accuracy in our meta-regression analysis, this may have been due to the fact that, of the 11 included studies, only 4 were retrospective in nature. Furthermore, of these 4 studies, 1 of them accounted for the largest number of subjects included in the analysis, which represents a possible cause of heterogeneity. On the other hand, an examination of the funnel plot symmetry and nonsignificant Egger testing provides some support for a conclusion that selection of publications was not seriously biased.

The definition of recurrence used by the authors in each study is another potential source of heterogeneity. The majority of the studies defined recurrence as having at least grade 1 polyps³⁹ on nasal endoscopy during the postoperative period. It remains unclear whether or not this is clinically significant. Other authors used more clinical definitions to define recurrence, such as need for revision surgery, prolonged postoperative systemic steroid requirements or persistent disease, and sinus symptoms, despite maximal medical management involving use of systemic steroids.

There are some important factors that must be considered when quantifying HTE histologically. Despite its common use in other eosinophilic-related disorders, the technique of counting the number of cells per HPF is currently not well standardized.⁴⁰ The number of slides used, level of magnification, field area size, and variable distribution of cells with the tissue itself may introduce additional variability. This resulted in the need to contact several authors to verify the definition of HPF they used in their publication. In addition, HTE as a tool to identify ECRS patients requires tissue to obtain a diagnosis. However, considering the usual severity of initial disease presentation associated with HTE, the majority of these ECRS patients will require surgery allowing for effective tissue sampling. If we can eventually find more effective and nonsurgical treatments, there is always the possibility of doing an in-office biopsy.

Another important factor to consider is the use of oral steroids. If given perioperatively, steroids may artificially lower the value of tissue eosinophilia. Within our meta-analysis, some authors excluded all patients with recent use of systemic steroids, whereby other authors had patients on maximal medical management, including systemic steroids preoperatively. Clinicians must therefore take this into consideration if they are to use HTE as a tool to predict recurrence within their CRS population. The relationship between perioperative steroid use and overall effect on tissue eosinophilia is a question that remains to be answered with certainty.

Clinical implications

As previously described, the most significant aspect of ECRS patients is their resistance to current interventions and higher likelihood of recurrence. Effectively diagnosing ECRS may provide clinicians with valuable information related to prognosis and management. For prognostication, clinicians may choose to monitor ECRS patients more closely for recurrence. For surgical management, if these patients do have a recurrence, clinicians may consider performing a more aggressive “full-house” ESS, with some evidence demonstrating greater overall effective outcomes after revision sinus surgeries.⁴¹ With regard to medical management, clinicians may also consider prescribing these patients more aggressive postoperative medical regimens.⁴² In addition, there is also the possibility of identifying new and more effective treatment options for this subgroup. This may include biologics, such as omalizumab and mepolizumab, which are both monoclonal antibodies that specifically target and reduce the overall eosinophilic inflammatory response.^{42,43}

Conclusion

Our findings suggest that using eosinophils per standardized high-power field has good diagnostic accuracy and may be a useful tool for predicting recurrence in patients with CRS. We feel strongly that this may help in prognostication and management and therefore encourage otolaryngologists to obtain sinus tissue samples for eosinophil quantification. In general, based on the results of our meta-analysis, we recommend a cut-off value of >55 eos/HPF be used for predicting the likelihood of recurrence of ECRS. These results are based on a different number of studies for each cut-off score, some of which included varied populations with different methodological characteristics. The same cut-off score may consequently not be appropriate in all settings. Further research is needed to investigate this difference based on geographic location. 🌐

References

- Meltzer EO, Hamilos DL, Hadley JA, et al. Rhinosinusitis: establishing definitions for clinical research and patient care. *J Allergy Clin Immunol*. 2004;114(suppl):155-212.
- Fokkens W, Lund V, Mullol J. EP305 2007: European position paper on rhinosinusitis and nasal polyps 2007. A summary for otorhinolaryngologists. *Rhinology*. 2007;45:97-101.
- Chan Y, Kuhn FA. An update on the classifications, diagnosis, and treatment of rhinosinusitis. *Curr Opin Otolaryngol Head Neck Surg*. 2009;17:204-208.
- Ishitoya J, Sakuma Y, Tsukuda M. Eosinophilic chronic rhinosinusitis in Japan. *Allergol Int*. 2010;59:239-245.
- Snidvongs K, Chin D, Sacks R, et al. Eosinophilic rhinosinusitis is not a disease of ostiomeatal occlusion. *Laryngoscope*. 2013;123:1070-1074.
- Snidvongs K, McLachlan R, Chin D, et al. Osteitic bone: a surrogate marker of eosinophilia in chronic rhinosinusitis. *Rhinology*. 2012;50:299-305.
- Ferguson BJ. Categorization of eosinophilic chronic rhinosinusitis. *Curr Opin Otolaryngol Head Neck Surg*. 2004;12:237-242.
- Ikeda K, Shiozawa A, Ono N, et al. Subclassification of chronic rhinosinusitis with nasal polyp based on eosinophil and neutrophil. *Laryngoscope*. 2013;123:E1-9.
- Kim SY, Park JH, Rhee CS, et al. Does eosinophilic inflammation affect the outcome of endoscopic sinus surgery in chronic rhinosinusitis in Koreans? *Am J Rhinol Allergy*. 2013;27:e166-9.
- Matsuwaki Y, Ookushi T, Asaka D, et al. Chronic rhinosinusitis: risk factors for the recurrence of chronic rhinosinusitis based on 5-year follow-up after endoscopic sinus surgery. *Int Arch Allergy Immunol*. 2008;146(suppl 1):77-81.
- Nakayama T, Yoshikawa M, Asaka D, et al. Mucosal eosinophilia and recurrence of nasal polyps—new classification of chronic rhinosinusitis. *Rhinology*. 2011;49:392-396.
- Tosun F, Arslan HH, Karslioglu Y, et al. Relationship between postoperative recurrence rate and eosinophil density of nasal polyps. *Ann Otol Rhinol Laryngol*. 2010;119:455-459.
- Georgalas C, Cornet M, Adriaenssens G, et al. Evidence-based surgery for chronic rhinosinusitis with and without nasal polyps. *Curr Allergy Asthma Rep*. 2014;14:427.
- Lou H, Meng Y, Piao Y, et al. Predictive significance of tissue eosinophilia for nasal polyp recurrence in the Chinese population. *Am J Rhinol Allergy*. 2015;29:350-356.
- DeConde AS, Mace JC, Levy JM, et al. Prevalence of polyp recurrence after endoscopic sinus surgery for chronic rhinosinusitis with nasal polyposis. *Laryngoscope*. 2017;127:550-555.
- Kountakis SE, Arango P, Bradley D, et al. Molecular and cellular staging for the severity of chronic rhinosinusitis. *Laryngoscope*. 2004;114:1895-1905.
- Snidvongs K, Lam M, Sacks R, et al. Structured histopathology profiling of chronic rhinosinusitis in routine practice. *Int Forum Allergy Rhinol*. 2012;2:376-385.
- Soler ZM, Sauer D, Mace J, Smith TL. Impact of mucosal eosinophilia and nasal polyposis on quality of life outcomes after sinus surgery. *Otolaryngology*. 2010;142:64-71.
- Soler ZM, Sauer DA, Mace J, Smith TL. Relationship between clinical measures and histopathologic findings in chronic rhinosinusitis: a 3-year prospective observational study. *Am J Rhinol Allergy*. 2014;28:260-264.
- Vlaminck S, Vauterin T, Hellings PW, et al. The importance of local eosinophilia in the surgical outcome of chronic rhinosinusitis: a 3-year prospective observational study. *Am J Rhinol Allergy*. 2014;28:260-264.
- Grgic MV, Cupic H, Kalogjera L, Baudoin T. Surgical treatment for nasal polyposis: predictors of outcome. *Eur Arch Otorhinolaryngol*. 2015;272:3735-3743.
- Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097.
- Sun DI, Joo YH, Auo HJ, Kang JM. Clinical significance of eosinophilic cationic protein levels in nasal secretions of patients with nasal polyposis. *Eur Arch Otorhinolaryngol*. 2009;266:981-986.
- Tokunaga T, Sakashita M, Haruna T, et al. Novel scoring system and algorithm for classifying chronic rhinosinusitis: the JESREC Study. *Allergy*. 2015;70:995-1003.
- Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. 2011;155:529-536.
- Reitsma JB, Glas AS, Rutjes AW, et al. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol*. 2005;58:982-990.
- Walter SD. Properties of the summary receiver operating characteristic (SROC) curve for diagnostic test data. *Stat Med*. 2002;21:1237-1256.
- Simundic AM. Measures of diagnostic accuracy: basic definitions. *EJIFCC*. 2009;19:203-311.
- Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ (Clin Res Ed)*. 2003;327:557-560.
- Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clin Res Ed)*. 1997;315:629-634.
- Brescia G, Marioni G, Franchella S, et al. A prospective investigation of predictive parameters for post-surgical recurrences in sinonasal polyposis. *Eur Arch Otorhinolaryngol*. 2016;273:655-660.
- Brescia G, Marioni G, Franchella S, et al. Can a panel of clinical, laboratory, and pathological variables pinpoint patients with sinonasal polyposis at higher risk of recurrence after surgery? *Am J Otolaryngol*. 2015;36:554-558.
- Do TQ, Barham HP, Earls P, et al. Clinical implications of mucosal remodeling from chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2016;6:835-840.
- Nakayama T, Asaka D, Kanaya H, et al. Prognostic factors for recurrence after endoscopic sinus surgery for chronic rhinosinusitis with nasal polyps. *Auris Nasus Larynx*. 2016;43:641-647.
- Snidvongs K, Pratt E, Chin D, et al. Corticosteroid nasal irrigations after endoscopic sinus surgery in the management of chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2012;2:415-421.
- Glas AS, Lijmer JG, Prins MH, et al. The diagnostic odds ratio: a single indicator of test performance. *J Clin Epidemiol*. 2003;56:1129-1135.
- Lee S, Lane AP. Chronic rhinosinusitis as a multifactorial inflammatory disorder. *Curr Infect Dis Rep*. 2011;13:159-168.
- Petit DB. Approaches to heterogeneity in meta-analysis. *Stat Med*. 2001;20:3625-3633.
- Meltzer EO, Hamilos DL, Hadley JA, et al. Rhinosinusitis: developing guidance for clinical trials. *J Allergy Clin Immunol*. 2006;118(suppl):S17-61.
- Dellon ES, Aderoju A, Woosley JT, et al. Variability in diagnostic criteria for eosinophilic esophagitis: a systematic review. *Am J Gastroenterol*. 2007;102:2300-2313.
- Shen PH, Weitzel EK, Lai JT, et al. Retrospective study of full-house functional endoscopic sinus surgery for revision endoscopic sinus surgery. *Int Forum Allergy Rhinol*. 2011;1:498-503.
- Ocampo CJ, Peters AT. Medical therapy as the primary modality for the management of chronic rhinosinusitis. *Allergy Asthma Proc*. 2013;34:132-137.
- Tajiri T, Matsumoto H, Hiraumi H, et al. Efficacy of omalizumab in eosinophilic chronic rhinosinusitis patients with asthma. *Ann Allergy Asthma Immunol*. 2013;110:387-388.