REVIEW ARTICLE

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Personalizing sinus surgery: a systematic review and meta-analysis of clinical and genetic predictors of outcome in chronic rhinosinusitis

Abbas Ardalan[1,2], Sahar Adl[1], Kosar Moarefvand[3], Elham Amirkhani[4], Sepehr Faridazar[5], Massoud Houshmand[6]

[1]Department of Biology, Arak University, Arak, [2]Armitagen Laboratory, Tehran, Iran, [3]I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University), Moscow, Russia, [4]Kashan university of Medical Sciences, Kashan, Iran, [5]Department of Anatomy, George Washington University, Washington, D.C., USA, [6]National Institute of Genetic Engineering and Biotechnology, Tehran, Iran

Abstract (J Korean Assoc Oral Maxillofac Surg 2026;52:58-72)

Approximately 25% of patients with chronic rhinosinusitis (CRS) have recurrence after endoscopic sinus surgery (ESS). The goal is to analyze and integrate research on individual and genetic factors of recurrence in CRS patients following ESS. A systematic review and meta-analysis were performed using PRISMA criteria. Various databases were searched from January 2008 to May 2025. ESS studies with adults with CRS reported results based on clinical or genetic factors. The Newcastle–Ottawa Scale and five dimensions of bias were examined study quality. Pooled odds ratios with 95% confidence intervals were estimated using a random-effects DerSimonian–Laird model. Heterogeneity was assessed using I^2, publication bias using funnel plots and Egger test, and evidentiary certainty using GRADE. A total of 17 trials with 40,059 individuals were examined. Asthma, non-steroidal anti-inflammatory drug (NSAID) intolerance, allergy, and higher Lund–Mackay scores (LMSs) were significant clinical predictors of recurrence. TAS2R38 polymorphisms had poorer outcomes, but only 4 trials were included. Asthma, NSAID intolerance, allergy, higher LMS, and TAS2R38 polymorphisms are significant predictors of recurrence in CRS following ESS. These results support the use of comorbidities, radiologic severity, and genetic biomarkers in preoperative risk classification, emphasizing the need for larger, standardized, and multi-ethnic research.

Key words: Chronic rhinosinusitis, Endoscopic sinus surgery, Recurrence, Genetic biomarkers, Predictors

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I. Introduction

Chronic rhinosinusitis (CRS) is a very common chronic inflammatory illness of the upper respiratory tract that affects 5% to 12% of the general population, according to epidemiological data[1]. The major way it affects patients is through quality of life reductions because of symptoms, including nasal congestion, hyposmia, facial pain, and chronic discharge, all of which also pose considerable financial burden on healthcare systems[2]. First-line intervention for CRS typically includes topical corticosteroids, saline nasal rinses, and antibiotics in some cases, however endoscopic sinus surgery (ESS) is valuable for patients who do not respond to these treatment approaches[3]. Even with advances in techniques for ESS, the outcomes for surgery are highly variable among patients. Some patients may see substantial changes in their symptoms and quality of life, while others see recurrences or revision surgery. Studies have shown that up to 25% of recurrences in the population of patients with CRS may be managed with revision surgery[4,5]. Notably, the patient population suffering from nasal polyps (CRS with nasal polyps, CRSwNP) usually has a worse disease phenotype, higher rates of recurrence, and more indications for revision surgery compared to their non-polyp counterparts (CRS without nasal polyps, CRSsNP).

This variety in findings has led researchers to study factors that predict the success of ESS. These factors are divided into two main categories: individual characteristics (asthma, allergies, disease severity via computed tomography [CT] scores, and the presence of nasal polyps) and genetic characteristics (gene variants that are associated with inflammatory

Massoud Houshmand
National Institute of Genetic Engineering and Biotechnology, Pajoohesh Blvd, Shahrak-e-Pajoohesh, Tehran 14977-16316, Iran
TEL: +98-21-4478-7301
E-mail: Prof.mhoushmand@gmail.com
ORCID: https://orcid.org/0009-0009-4319-0186

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and immune responses)[6]. Asthma and non-steroidal anti-inflammatory drug (NSAID) intolerance (aspirin-exacerbated respiratory disease, AERD) are significant predictors of recurrence after ESS. Loftus et al.[5] reported in a meta-analysis that asthma patients were 1.8 times more likely to require revision surgery compared to those without asthma. In addition, illness severity assessed with radiographic assessments (e.g., Lund–Mackay score [LMS]) and the occurrence of nasal polyps correlate with poorer ESS outcomes[7]. Recent literature has increasingly valued genetic markers in CRS and response to ESS. Researchers have explored inflammation gene polymorphisms (such as IL-1A, IL-1β, and TNF-α) and taste receptors (taste receptor 2-member 38 gene, TAS2R38) involved in innate respiratory defense as factors regarding disease severity and surgical outcomes[8,9].

Taste receptors, especially TAS2R38, have drawn attention for their role in detecting Gram-negative bacteria and in generating nitric oxide (NO) to enhance mucociliary clearance and antibacterial capacity. Adappa et al.[8] reported an impaired response to ESS and a greater rate of relapse among individuals with the inactive (AVI/AVI) TAS2R38 genotype. However, the evidence has not consistently supported this area. Some studies report no association between the TAS2R38 genotype and ESS[10]. These shortcomings, presented in some of the contradictory findings such as small sample sizes, short follow-up, and methodology differences, indicate that a meta-analysis could potentially pool data and consolidate evidence[11]. A meta-analysis will create a larger statistical sample from several studies and investigate heterogeneity in those studies to better understand the determinants of ESS success[12].

Accordingly, this study provides a comprehensive systematic review and meta-analysis to evaluate both clinical (e.g., asthma, allergy, LMSs, etc.) and genetic (e.g., TAS2R38 polymorphisms) predictors of recurrence following ESS in CRS patients. Our goal is to strengthen the evidence base for risk stratification, inform clinical decision-making, and guide future research on personalized management strategies in CRS.

II. Materials and Methods

This systematic review and meta-analysis were performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement in order to improve the transparency and quality of reporting[13]. The protocol for this study has been registered on the PROSPERO database (registration number: CRD420251114988).

1. Study design and literature search

This research was undertaken as a systematic review and meta-analysis to explore individual and genetic factors of ESS success in individuals with CRS. A comprehensive literature search was completed through PubMed, Scopus, Web of Science, and Google Scholar. The literature search was conducted for the past 17 years, between January 2008 and May 2025, to include more recent and relevant literature. Specifically, the phrases “chronic rhinosinusitis”, “endoscopic sinus surgery”, “ESS outcomes,” “predictor/s of surgical success”, “genetic polymorphisms”, “TAS2R38”, “individual factors”, “asthma”, and “Allergy”, were used. along with hand-searching the reference lists of relevant papers to find additional studies.

Although the search was comprehensive up to May 2025, it is possible that some relevant studies were missed due to indexing delays or database limitations.

2. Inclusion and exclusion criteria

Studies that met the following criteria were included in this meta-analysis: (1) studied patients with CRS who underwent ESS, (2) examined individual (e.g., asthma, allergies, or disease severity) or genetic (e.g., gene polymorphisms) predictors of ESS success, (3) provided quantitative data such as changes in quality-of-life scores (22-item Sino-Nasal Outcome Test, SNOT-22), recurrence rates, or allele frequencies, (4) published between 2008 and 2025, and (5) had a case-control, cohort, or meta-analytic design. Studies including CRS patients (with or without nasal polyps) were eligible, but subgroup-specific data were not required. Studies that did not provide sufficient data to extract an effect (e.g., odds ratio [OR] or confidence interval [CI]), studies with a sample size of less than 20 people, and studies published in languages other than English were excluded from the analysis. Although inflammatory gene polymorphisms such as IL-1α, IL-1β, and TNF-α have been reported in the literature, these were not included in the pooled analysis because only one or two studies were available, and quantitative data were insufficient for meta-analysis.

3. Study selection

Two members of the investigative team (A. A. and E. A.)

first independently screened the titles and abstracts of studies identified. Next, they reviewed the full text of those articles that appeared to meet the inclusion criteria. Any disagreements between members of the research team were resolved through discussion or consulting a third member of the team. The study selection process was recorded using the PRISMA flow diagram, as it clearly demonstrated the steps of screening and selection.

4. Data extraction

Data were extracted independently by two investigators, and any discrepancies were resolved by discussion and consensus. The extracted information included author name, year of publication, study site, study type, study population (number of patients and controls), predictors examined (individual or genetic), ESS success measures (such as SNOT-22 changes, recurrence rate, or improvement in sense of smell), and effect size (OR and 95% CI). For studies where OR and CI were not directly reported, raw data (such as number of patients per group or difference in allele frequencies) were extracted and used to calculate OR[14,15].

5. Assessment of quality and bias

The Newcastle–Ottawa Scale (NOS), which is suitable for cohort and case-control studies, was used to assess the study's quality. The tool has three domains: Selection, Comparability, and Outcome/Exposure, with a maximum score of 9. A score of 7 and above was determined to be a high-quality study. RoB was assessed across five domains (D1-D5), and judgments were categorized as low risk, some concerns, or high risk, summarized graphically with robvis.

6. Statistical analysis

For meta-analysis, data were analyzed using R (version 4.5.0; R Foundation) with meta and meta for packages. Effect sizes were calculated as ORs and 95% CIs for individual and genetic predictors. For studies that did not specify ORs, we used raw data (e.g., number of patients or differences in allelic frequencies) to calculate ORs. The I^2 statistic was used to assess heterogeneity among studies. The Random-effects DerSimonian–Laird model was utilized for the heterogeneity (I^2>50%). Sensitivity analysis was also performed to assess the impact of studies with high risk of bias (RoB) on the overall results. To examine publication bias, the funnel plot and Egger test were used. The statistical significance level (*P*-value) was considered less than 0.05. Certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, and summary of findings tables were generated with MAGICapp (https://app.magicapp.org/).

7. Ethical considerations

This study did not require ethical approval, as it only used previously published data. However, all procedures were conducted in accordance with the principles of the Declaration of Helsinki.

III. Results

A total of 130 articles were identified; after removing 27 duplicate articles, 103 articles were included in the title and abstract screening. Of these, 55 articles were selected for full-text review. Finally, 17 articles were included in the final analysis. The details of the selection are shown in the PRISMA diagram[16].(Fig. 1)

1. Study characteristics

Between 2008 and 2025, evidence was aggregated from various study designs, including cohort and case-control studies, as well as prospective and retrospective observational research. Additionally, one prior meta-analysis was incorporated. The study population was composed of patients diagnosed with CRS who had undergone ESS, commonly referred to as functional endoscopic sinus surgery (FESS) in the literature. In these investigations, correlations between individual characteristics, genetic markers, and postoperative outcomes were examined. Both CRS phenotypes—CRSwNP and CRSsNP—were represented, although in several studies these subgroups were not reported separately, leading to incomplete subgroup data. A total of 40,059 participants were included in the dataset, constituting a substantial sample size that lends considerable statistical power to the primary comparisons. The evaluated predictors encompassed individual factors such as asthma, allergy, NSAID intolerance, LMS, and peripheral blood eosinophilia, in addition to genetic factors including TAS2R38 polymorphisms, as outlined in Table 1.

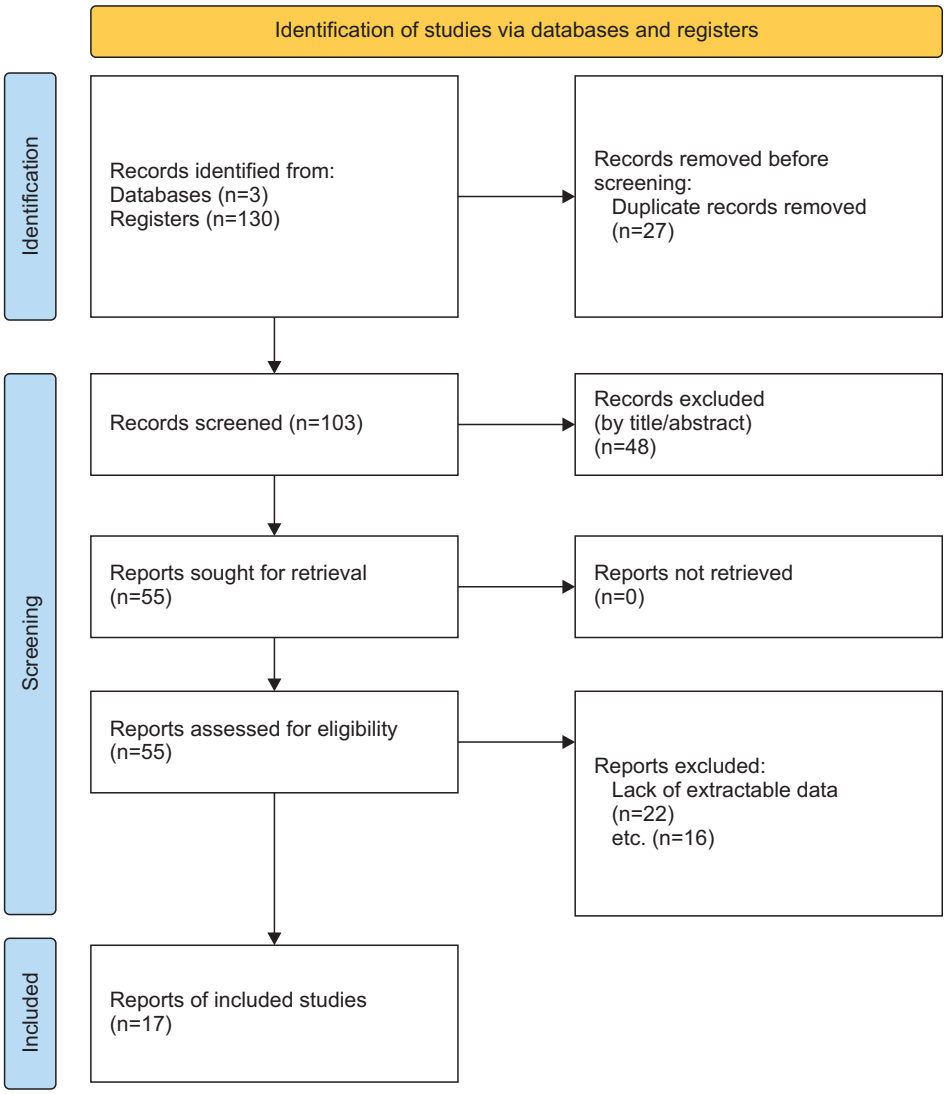


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.
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2. Assessment of study quality (RoB assessment)

The assessment was performed with the NOS tool. Most studies were of moderate to good quality. High-risk studies usually had small sample sizes and inadequate controls.(Table 2, Fig. 2) The funnel plot (Fig. 3) indicates potential publication bias in the asthma studies because of the asymmetrical distribution. This observation is also consistent with the results of Egger test.

1) Funnel plot interpretation

Looking across the six predictors, the funnel plots told a mixed story. Asthma and NSAID intolerance were pretty much mirror-symmetric—about as clean as one hopes—suggesting little publication bias. Eosinophils and allergy showed some spread, a bit messy, but not obviously skewed. In contrast, the LMS and—especially—TAS2R38 displayed a noticeable tilt, the sort of pattern that hints at small-study effects or selective publication. See Fig. 3; the pictures make the point faster than words.

To probe small-study effects, we ran Egger test for each predictor. The signal wasn't uniform. Asthma cleared the significance bar (t=2.420, P=0.046), the LMS did as well (t=5.144, P=0.014), and peripheral eosinophils lit up strongly, in fact (t=56.844, P<0.001). Allergy showed no such pattern (P=0.440); same story for NSAID intolerance (P=0.844) and the TAS2R38 polymorphism (P=0.996). In short, Egger test points to possible publication bias for asthma, LMS, and peripheral eosinophils, while we find no convincing evidence for allergy, NSAID intolerance, or TAS2R38.(Table 3)

Table 1. Summary of information from the studies used

Study	Study location	Study type	Study population	Predictors assessed	ESS outcome
Wu et al.[17] (2020)	Taiwan	Prospective cohort study	CRS patients underwent ESS (n=84)	Asthma, Allergy, LMSs	Revision rate (5 years): 19.05% Mean time to revision: ~25 months Key predictors: Nasal allergy (OR=9.29) and high LMS (OR=1.29) LMS cutoff: >13.5 (AUC=0.79, Sensitivity=93.75%) Worst outcome: Patients with both nasal allergy and LMS ≥14 had only 38.1% revision-free survival.
Lilja et al.[7] (2022)	Italy	Prospective observational study	CRS patients underwent ESS (n=44)	CT scores, asthma, AERD, allergy, Smoking status, eosinophilia, prior surgery	QoL improvement measured by SNOT-22 Significant improvement postoperatively (P<0.001) No significant effect from nasal polyps, asthma, allergy, smoking, eosinophilia, aspirin sensitivity, systemic disease, or previous surgery on surgical outcomes SNOT-22 was not significantly correlated with preoperative CT scores
Lilja et al.[18] (2025)	Italy	Cohort study	CRS patients (CRSwNP) post-ESS (n=237)	Asthma, AERD, CT scores, age, sex, BMI, allergy, smoking, prior sinus surgeries	Revision surgery rate: 46% Median time to revision: 4.8 years Independent predictors of revision: asthma (HR=2.03, P=0.003), NERD (HR=2.34, P=0.001), LMS >17 (HR=2.16, P=0.006) Cumulative revision-free survival: significantly lower in patients with asthma, NERD, or high CT scores
Veloso-Teles and Cerejeira[22] (2017)	Portugal	Retrospective observational study	CRS patients (CRSwNP) undergoing ESS (n=85)	Occupational dust exposure, non–IgE-mediated asthma, Age, sex, IgE-mediated asthma, allergic rhinitis, smoking, LMS, polyp endoscopic grade, post-op corticosteroid use	ESS led to significant symptom improvement in patients with CRS with nasal polyps, particularly in nasal obstruction. Over an average follow-up of 35.1 months, 31% experienced polyp recurrence, and 7% required revision surgery. The strongest predictors of recurrence were occupational dust exposure (OR=38.0, 95% CI 4.18-345.69) and non–IgE-mediated asthma (OR=8.65, 95% CI 1.62-46.16). The predictive model showed high accuracy (AUC=0.822).
Loftus et al.[5] (2020)	USA	Retrospective cohort study	CRS patients underwent ESS (CRSwNP) (n=34,000)	Asthma, polyps, comorbidities, AERD, AFRS	Revision surgery rate: 17.4% Higher revision rates associated with: asthma (HR=2.1), AERD (HR=2.9), AFRS (HR=3.0), prior ESS (HR=1.6), greater surgical extent (e.g., frontal sinusotomy: HR=2.3) Median time to revision: not specified in summary, but cumulative hazard increases notably over 10 years
Asaka et al.[29] (2012)	Japan	Prospective cohort study	CRS patients undergoing ESS (n=706)	Age, sex, laterality, anesthesia type, prior sinus surgery, eosinophil count, IgE, asthma, vascular disease, nasal polyp score, LMS	Complications in 5.8% of patients; asthma and higher nasal polyp score were independent risk factors; 0.1% major complication rate (CSF leak), 5.7% minor complications (mostly hemorrhage and orbital injury)
Jeruzal-Świątecka et al.[21] (2024)	Poland	Case-control study	106 CRSwNP patients vs. 438 controls	TAS2R38 gene polymorphisms (rs713598, rs1726866, rs10246939); PTC tasting; Clinical data (VAS, SNOT-22, CT, endoscopy); allergy, asthma status	AVI/AVI diplotype associated with more severe disease (higher VAS, lower QoL); PAV/PAV associated with milder CT findings and potential protective effect; No significant differences for other clinical features except year-long allergy in PAV/PAV individuals (P=0.0431)
Koskinen et al.[31] (2016)	Finland	Retrospective cohort study	CRS patients underwent ESS (n=646)	Age, sex, asthma, NERD, allergic rhinitis, eosinophilia, preoperative CT score, smoking, prior surgery	Revision surgery rate: 20%; higher revision risk in patients with NERD, asthma, and previous surgery; male gender and age <40 also linked to higher risk; eosinophilia correlated with recurrence

Table 1. Continued

Study	Study location	Study type	Study population	Predictors assessed	ESS outcome
Matsuwaki et al.[23] (2008)	Japan	Retrospective cohort study	CRS patients undergoing ESS (n=65)	Peripheral eosinophilia (≥520/μL), asthma, mucosal eosinophilia (≥120/HPF), post-ESS infection, total IgE, CT score, nasal polyps, fungi, allergic rhinitis, age, gender	Recurrence in 16.1% of patients; mucosal eosinophilia (ECRS diagnosis) was the strongest predictor of recurrence; asthma and peripheral eosinophilia also predictive; total IgE, polyps, CT score, fungi, allergic rhinitis not predictive
Juan et al.[30] (2017)	China	Retrospective cohort study	CRS patients undergoing FESS (n=288)	Age, allergic rhinitis, severity of dysosmia, history of nasosinusitis, long-term use of nasal decongestant, comprehensive therapy after surgery	64.9% fully recovered; 25% improved; 10.1% untreated; age ≥60, allergic rhinitis, dysosmia, prior nasosinusitis, and long-term decongestant use were risk factors; comprehensive therapy was protective
Stryjewska-Makuch et al.[25] (2019)	Poland	Prospective observational study	CRS patients (CRSwNP) with undergoing ESS (n=72)	Asthma, allergy, ASA hypersensitivity, nasal polyps, eosinophili	All patients improved postoperatively; significantly poorer outcomes in patients with asthma, ASA hypersensitivity, and eosinophilia; allergic rhinitis and nasal polyps also linked to worse subjective improvement
Adappa et al.[14] (2013)	USA	Pilot observational genetic study	CRS patients undergoing primary FESS (n=28)	T2R38 genotype (PAV/PAV, PAV/AVI, AVI/AVI)	Supertasters (PAV/PAV) less likely to require surgery; lower need for antibiotics post-op among supertasters
Adappa et al.[8] (2014)	USA	Prospective cohort study	70 CRS patients undergoing primary FESS and 347 control	TAS2R38 genotype (PAV/PAV, AVI/PAV, AVI/AVI), comorbidities (asthma, allergies, polyps, aspirin sensitivity, diabetes, smoking)	TAS2R38 AVI/AVI genotype significantly overrepresented in patients requiring ESS, suggesting it's an independent risk factor
Adappa et al.[15] (2016)	USA	Prospective cohort study	123 patients with CRS undergoing ESS	TAS2R38 genotype (PAV/PAV, PAV/AVI, AVI/AVI), PTC taste sensitivity, polyp status, age, gender, race, asthma, allergies, aspirin sensitivity, diabetes, smoking, LMS	Overall SNOT-22 improvement at 6 months: 25±23; CRSsNP PAV/PAV: 38±21 vs. non-PAV/PAV: 12±22 (P=0.006); CRSwNP similar improvement across genotypes; multivariate regression (n=207) confirmed PAV/PAV significance in CRSsNP (P=0.001), polyp interaction (P=0.007); PTC sensitivity correlated with CRSsNP outcomes (P=0.03)
Brunet et al.[32] (2023)	Canada	Ambispective observational study	CRS patients (CRSwNP) post-ESS (n=62)	NSAID intolerance, asthma, EPS, RS, age, sex, allergy, smoking status	Mean score: 39.8 (moderate–severe QoL impact) Top symptoms: smell/taste loss, nasal blockage, runny nose Higher scores linked to: eosinophilia, IL-8 expression, NSAID intolerance, polyp size (EPS) Highest scores in: patients with asthma+NSAID intolerance
Abuduruk et al.[19] (2024)	Multi-national	Systematic review	CRS patients underwent (n=2,515)	Asthma, aspirin intolerance, peripheral eosinophilia, IL-5 expression, T2 profile, sinus opacification, younger age, male sex, prior ESS	Recurrence rates ranged from 13.4% to 66% across studies; multiple risk factors for recurrence were consistently found across geographic populations
Brescia et al.[20] (2016)	Italy	Prospective observational study	CRS patients)CRSwNP) undergoing FESS (n=143)	Age, allergy, asthma, NSAID intolerance (ASA syndrome), EGPA (Churg–Strauss), serum eosinophils and basophils, total and specific IgE, histological eosinophilic polyposis	Eosinophilic polyposis was the strongest independent predictor of recurrence (OR=2.92; P=0.033). Patients with eosinophilic polyps relapsed faster (median 15 vs. 25 months; P=0.003). Other univariate predictors: allergy, younger age, EGPA.

(CRS: chronic rhinosinusitis, ESS: endoscopic sinus surgery, LMS: Lund–Mackay score, OR: odds ratio, AUC: area under the curve, CT: computed tomography, AERD: aspirin-exacerbated respiratory disease, QoL: quality of life, SNOT-22: 22-item Sino-Nasal Outcome Test, CRSwNP: chronic rhinosinusitis with nasal polyps, BMI: body mass index, HR: hazard ratio, NERD: nonsteroidal anti-inflammatory drug–exacerbated respiratory disease, AFRS: allergic fungal rhinosinusitis, CSF: cerebrospinal fluid, PTC: phenylthiocarbamide tasting, VAS: visual analogue scale, HPF: high power field, ECRS: eosinophilic chronic rhinosinusitis, ASA: aspirin-sensitive asthma, CRSsNP: chronic rhinosinusitis without nasal polyps, NSAID: non-steroidal anti-inflammatory drug, EPS: endoscopic polyp score, RS: radiologic score, IL: interleukin)

Table 2. Newcastle–Ottawa scale (NOS) and risks of bias for studies

Study	Design	Selection (1-4)	Comparability (1-2)	Outcome/ exposure (1-3)	NOS score (max 9)	Risk of bias
Wu et al.[17] (2020)	Cohort study	☆☆☆	☆☆	☆☆	7	Moderate
Lilja et al.[7] (2022)	Cohort study	☆☆☆	☆☆	☆☆	7	Moderate
Lilja et al.[18] (2025)	Prospective cohort study	☆☆☆☆	☆☆	☆☆☆	9	Low
Veloso-Teles and Cerejeira[22] (2017)	Retrospective cohort study	☆☆☆	☆	☆☆	6	Moderate
Loftus et al.[5] (2020)	Retrospective cohort study	☆☆☆	☆	☆☆☆	7	Moderate
Asaka et al.[29] (2012)	Prospective cohort study	☆☆☆	☆	☆☆☆	7	Low–Moderate
Jeruzal-Świątecka et al.[21] (2024)	Case-control study	☆☆☆	☆	☆☆	6	Moderate
Koskinen et al.[31] (2016)	Retrospective cohort study	☆☆☆	☆☆	☆☆	7	Low
Matsuwaki et al.[23] (2008)	Retrospective cohort study	☆☆☆	☆	☆☆	6	Moderate
Juan et al.[30] (2017)	Retrospective cohort study	☆☆☆	☆	☆☆	6	Moderate
Stryjewska-Makuch et al.[25] (2019)	Retrospective cohort study	☆☆☆	☆	☆☆	6	Moderate
Adappa et al.[14] (2013)	Retrospective cohort study	☆☆☆	☆☆	☆☆	7	Low
Adappa et al.[8] (2014)	Prospective cohort study	☆☆☆	☆	☆☆	6	Moderate
Adappa et al.[15] (2016)	Prospective cohort study	☆☆☆☆	☆☆	☆☆☆	9	Low
Brunet et al.[32] (2023)	Case-control study	☆☆☆	☆☆	☆☆	7	Moderate
Abuduruk et al.[19] (2024)	Systematic review (not NOS applicable)	-	-	-	-	High (publication/ selection bias risk)
Brescia et al.[20] (2016)	Prospective observational study	☆☆☆	☆	☆☆☆	7	Low–Moderate

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Fig. 2. Risks of bias summary plot.
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3. Review of individual study results

1) Individual factors

Reports on clinical predictors of recurrence after ESS in CRS are a bit all over the place. Signals wobble across cohorts. Even so, two factors keep showing up with real consistency: asthma and NSAID intolerance. Asthma, especially, behaves like an independent driver of poor outcomes—more revisions, shorter disease-free intervals—repeated across studies[5,17]. NSAID intolerance tells a similar story, with multiple analyses backing its independent predictive value[18,19]. Allergy/atopy mixed. Statistically significant in some papers, not in others[17,20]. Not a clean win.

By contrast, the usual suspects—sex, smoking status, prior sinus surgery, occupational exposures—don't land consistently as risks. Some hints, plenty of shrugs. Taken together, asthma and NSAID intolerance are, on balance, the most dependable individual clinical flags for CRS recurrence after ESS.

2) Genetic factors

Variants in the TAS2R38 bitter-taste receptor were found to be associated with both CRS risk and postsurgical outcomes. Study participants with at least one fully functional genotype (PAV/PAV) appeared to have comparatively greater protection from developing disease and received greater improvements in post-operative quality-of-life scores compared to patients with nonfunctional variants, especially if they had no previous nasal polyps. This was generally in line with the theory of airway chemosensing contributing to mucosal defense; however, the mechanistic basis for this remains in contention. Conversely, nonfunctional genotypes (AVI/AVI genotype or

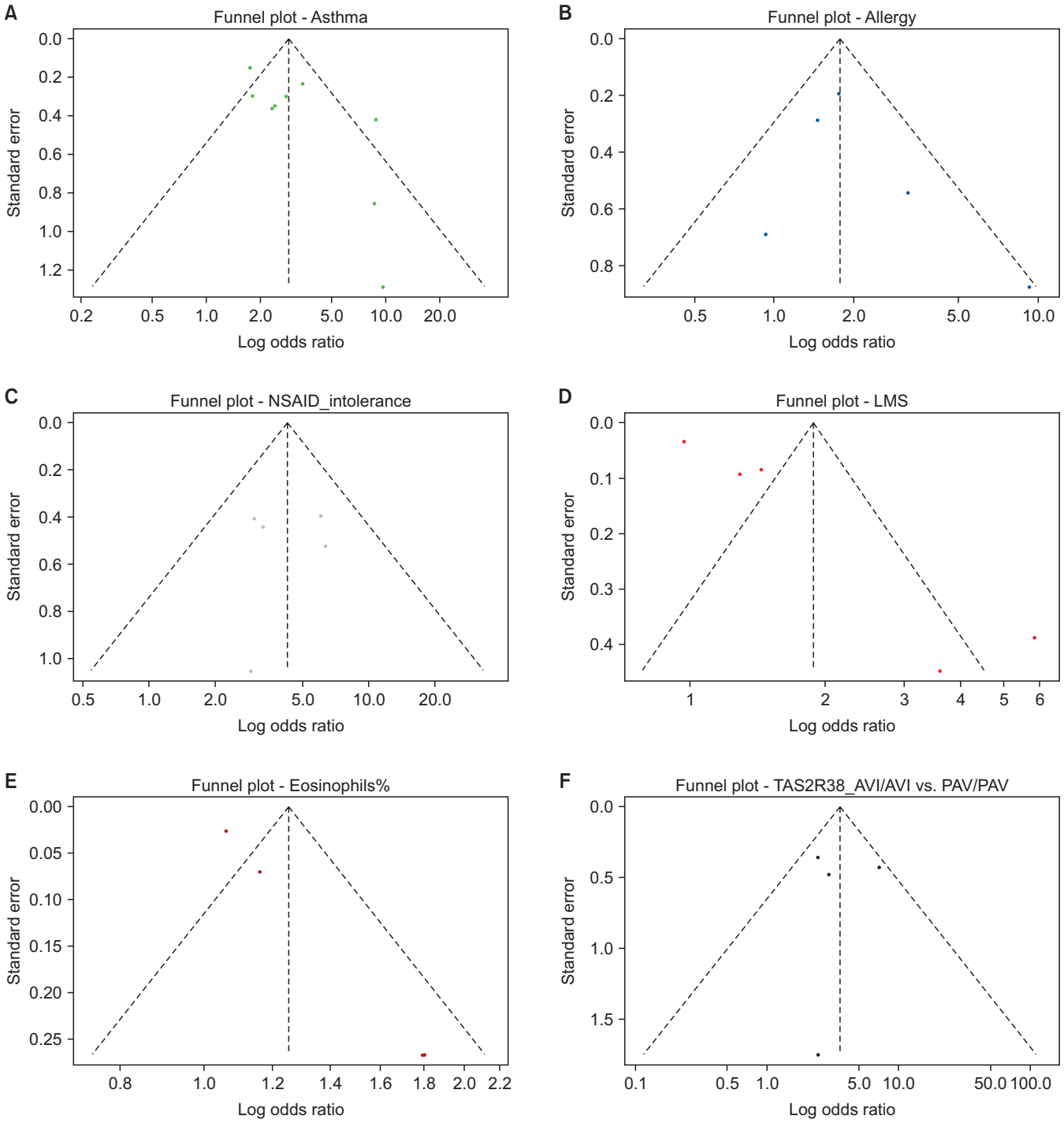


Fig. 3. Funnel plots for predictors of recurrence after endoscopic sinus surgery (ESS) in chronic rhinosinusitis (CRS). Each dot represents an individual study included in the meta-analysis. Symmetry was observed for allergy and non-steroidal anti-inflammatory drug (NSAID) intolerance, whereas some asymmetry was noted for asthma, eosinophils, Lund–Mackay score (LMS), and taste receptor 2-member 38 gene (TAS2R38).

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heterozygous variants) exhibited a strong association with worse outcomes and an increased likelihood of CRS[8,14,15,21].

4. Meta-analysis results

This meta-analysis consisted of 17 studies that explored individual and genetic factors associated with outcomes of

Table 3. Results of Egger test test for publication bias across predictors of recurrence after ESS in CRS

Predictor	k	*t*_stat	*P*-value	Significant
Asthma	9	2.420	0.046	Yes
Allergy	5	0.887	0.440	No
NSAID_intolerance	5	–0.215	0.844	No
LMS	5	5.144	0.014	Yes
Eosinophils	4	56.844	<0.001	Yes
TAS2R38_AVI/AVI vs. PAV/PAV	4	0.006	0.996	No

(ESS: endoscopic sinus surgery, CRS: chronic rhinosinusitis, NSAID: non-steroidal anti-inflammatory drug, LMS: Lund–Mackay score)

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ESS/FESS for patients with CRS. Factors included in this meta-analysis that were reported in at least four studies included asthma, allergy, NSAID sensitivity, LMS, eosinophils, and TAS2R38 genotype. The pooled ORs for each predictor variable are presented in the forest plot.(Fig. 4)

In the pooled analysis, several clinical predictors were identified for CRS recurrence following ESS. A strong and consistent association with recurrence was demonstrated for asthma (OR=2.87, 95% CI 2.01-4.10; *P*<0.001). The most substantial effect was observed for NSAID intolerance—

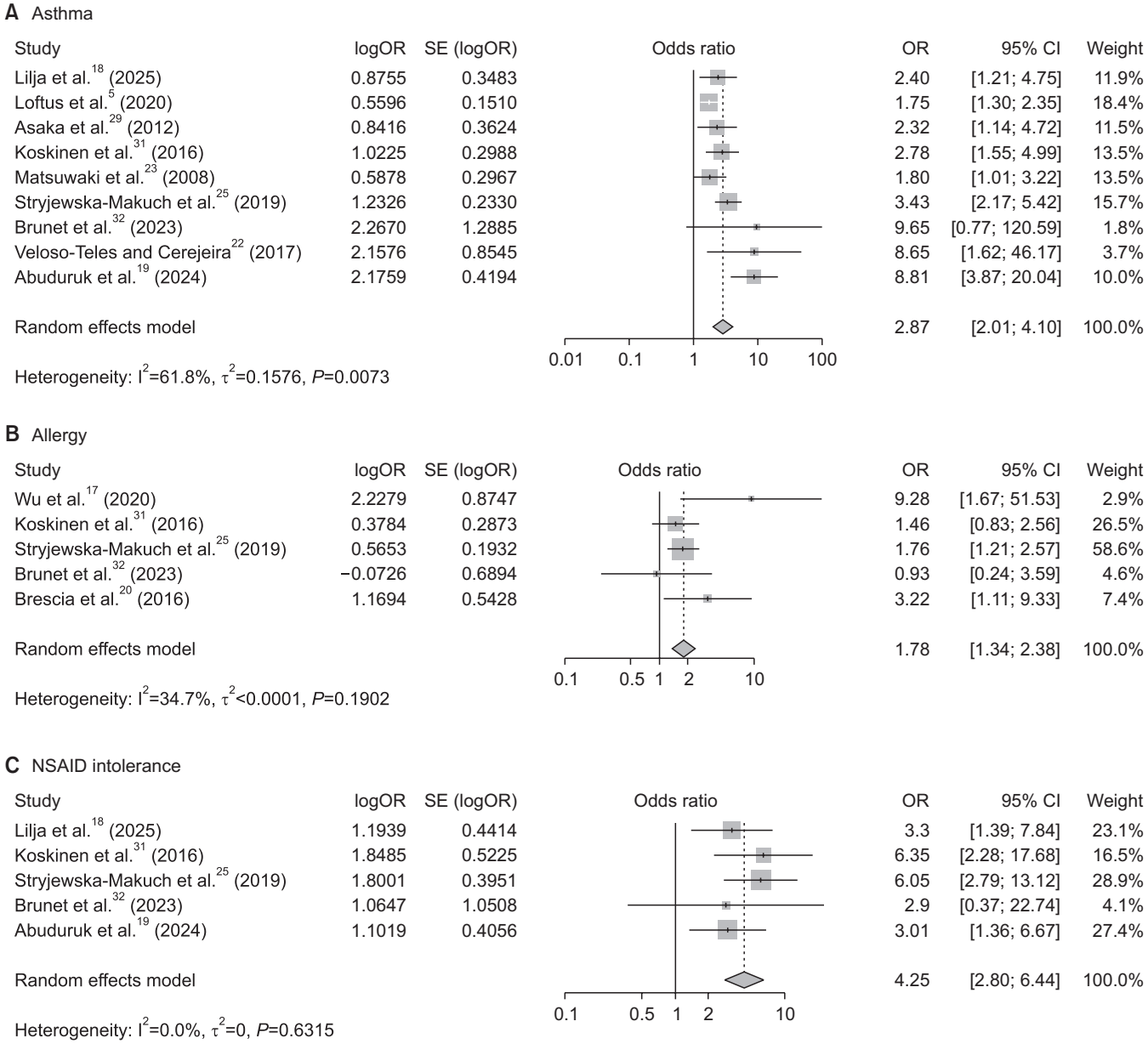


Fig. 4. Forest plots of pooled ORs with 95% CIs for predictors of recurrence after ESS in CRS. Each square represents an individual study, with the size proportional to its weight in the analysis; horizontal lines indicate 95% CIs. The diamond represents the overall pooled effect size. The vertical line corresponds to the null effect (OR=1). (OR: odds ratio, CI: confidence interval, SE: standard error, ESS: endoscopic sinus surgery, CRS: chronic rhinosinusitis)

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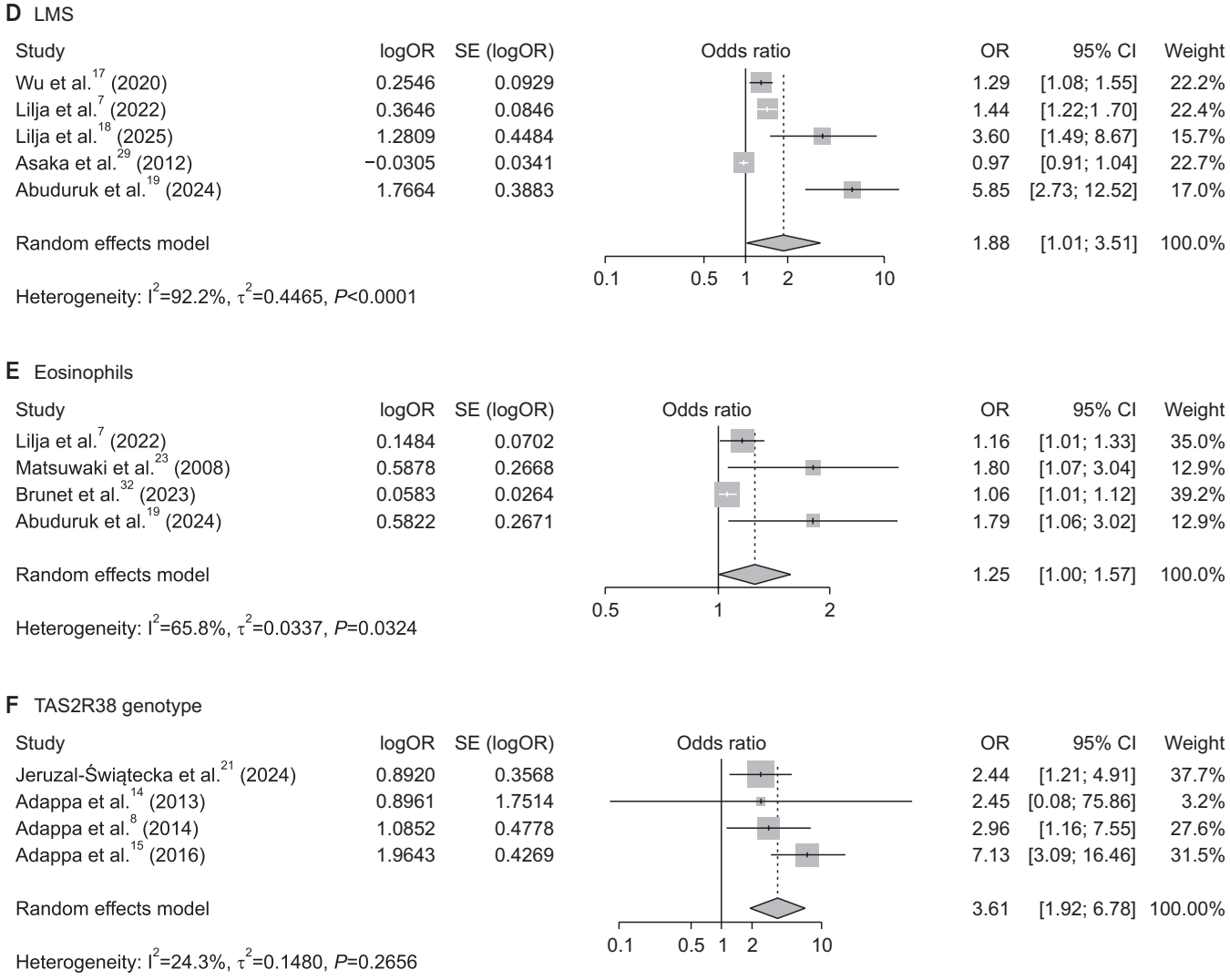


Fig. 4. Continued.
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aspirin-exacerbated respiratory disease (AERD)—(OR=4.25, 95% CI 2.80-6.44; *P*<0.001). Allergy was also found to be significantly associated with recurrence (OR=1.78, 95% CI 1.34-2.38; *P*<0.001). Higher LMS were associated with increased risk, although the effect size was more modest (OR=1.88, 95% CI 1.01-3.51; *P*=0.047). Peripheral blood eosinophilia demonstrated an elevated point estimate without reaching statistical significance in the overall model (OR=1.25, 95% CI 0.99-1.57; *P*=0.052). The effect direction was consistent across analyses; however, the evidence certainty remained limited.

In addition to clinical predictors, genetic variation in the bitter taste receptor TAS2R38 was also significantly associated with recurrence. Patients carrying the nonfunctional AVI/AVI genotype had a more than three-fold higher risk of recurrence compared with those with the functional PAV/PAV genotype (OR=3.61, 95% CI 1.92-6.78). The summary of predictors is presented in Table 4.

Table 4. Summary of findings from predictor analysis

Predictor	Odds ratio	95% confidence interval	*P*-value	I^2 (%)
Asthma	2.87	2.01-4.10	<0.001	61.79
Allergy	1.78	1.34-2.38	<0.001	34.66
NSAID intolerance	4.25	2.80-6.44	<0.001	0
LMS	1.88	1.01-3.51	0.047	92.17
Eosinophils	1.25	0.99-1.57	0.052	65.83
TAS2R38 genotype	3.61	1.92-6.78	<0.001	24.27

(NSAID: non-steroidal anti-inflammatory drug, LMS: Lund–Mackay score)
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Asthma (I^2=61.79%), eosinophils (I^2=65.83%), and LMS

Table 5. Summary of findings table generated using MAGICapp, based on the GRADE approach

Outcome (predictor of recurrence after ESS in CRS)	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of studies	Certainty of the evidence (GRADE)	Comment
	Risk with control	Risk with intervention				
Asthma	~20% recurrence	~40%-45% (95% CI: 35%-50%)	OR=2.87 (95% CI: 2.01-4.10)	9	⊕⊕⊕⊖ Moderate	Consistent results, low publication bias; downgraded for moderate RoB
Allergy	~20% recurrence	~30% (95% CI: 25%-35%)	OR=1.78 (95% CI: 1.34-2.38)	5	⊕⊕⊕⊖ Moderate	Mixed findings across studies, some inconsistency
NSAID intolerance	~20% recurrence	~55%-60% (95% CI: 45%-65%)	OR=4.25 (95% CI: 2.80-6.44)	5	⊕⊕⊕⊕ High	Strongest and most consistent predictor; robust across studies
LMS (high)	~20% recurrence	~35% (95% CI: 22%-48%)	OR=1.88 (95% CI: 1.01-3.51)	5	⊕⊕⊖⊖ Low	Limited number of studies; possible small-study effects
Peripheral eosinophils	~20% recurrence	~25% (95% CI: 20%-30%)	OR=1.25 (95% CI: 0.99-1.57)	4	⊕⊕⊖⊖ Low	Borderline significance; heterogeneity in definitions
TAS2R38 (AVI/AVI vs. PAV/PAV)	~20% recurrence (PAV/PAV)	~45% (95% CI: 30%-55%)	OR=3.61 (95% CI: 1.92-6.78)	4	⊕⊕⊖⊖ Low–Moderate	Significant in USA cohorts; not replicated in all populations
SNOT-22 improvement (functional vs. nonfunctional TAS2R38)	Mean Δ=12 (nonfunctional)	Mean Δ=38 (functional PAV/PAV)	SMD ≈ 1.21 (large effect)	5	⊕⊕⊖⊖ Low	Limited to one prospective cohort (Adappa et al.[8] [2015]), only significant in CRSsNP

Patient or population: Adults with CRS, including both patients with nasal polyps (CRSwNP) and without nasal polyps (CRSsNP), who underwent ESS.
Setting: Tertiary referral centers and university hospitals across multiple countries (USA, Europe, and Asia), published between 2008-2025.
Intervention: Presence of clinical comorbidities (asthma, NSAID intolerance, allergy, peripheral eosinophilia, higher LMSs) or genetic variation (TAS2R38 polymorphisms) as potential predictors of recurrence.
Comparison: Patients without these comorbidities or carrying the functional TAS2R38 genotype (PAV/PAV), serving as the reference group.
Key points:
• High certainty evidence: NSAID intolerance (AERD/NERD)
• Moderate certainty evidence: asthma, allergy
• Low certainty evidence: LMS, peripheral eosinophils, TAS2R38, SNOT-22 outcome
• Clinical comorbidities (asthma, AERD) are the strongest predictors; genetic markers (TAS2R38) show promise but need replication.
• High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
• Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
• Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
• Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

(GRADE: Grading of Recommendations, Assessment, Development, and Evaluation, LMS: Lund–Mackay score, ESS: endoscopic sinus surgery, TAS2R38: taste receptor 2-member 38 gene, CRSwNP: chronic rhinosinusitis with nasal polyps, CRSsNP: chronic rhinosinusitis without nasal polyps, NSAID: non-steroidal anti-inflammatory drug, CI: confidence interval, OR: odds ratio, RoB: risk of bias, AERD: aspirin-exacerbated respiratory disease, NERD: nonsteroidal anti-inflammatory drug–exacerbated respiratory disease)
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(I^2=92.17%) all had considerable heterogeneity. The heterogeneity was due in part to the heterogeneous definition of outcome across the studies, which varied between endoscopic recurrence, radiological recurrence, revision surgery, and quality-of-life difference. Meta-regression by follow-up duration was attempted but underpowered (P>0.1).

According to the GRADE assessment, the most consistent evidence was observed for NSAID intolerance (AERD/NERD) and asthma, both of which were identified as reliable predictors of recurrence after ESS in CRS. Allergy was associated with a moderate, but weaker effect. Higher LMS and peripheral blood eosinophil counts were associated with recurrence, though less so and with weaker certainty. TAS2R38 polymorphisms were associated with recurrence in certain cohorts; however, that data was weakened by very few studies and probably publication biases. Overall, clinical comorbidities provided better, stronger, and more clinically applicable predictors than laboratory or genetic indicators. (Table 5)

5. Conclusions from the meta-analysis

• Factors such as asthma, NSAID intolerance, allergy, and higher LMSs were significantly associated with recur-

rence after ESS.

- The genetic factor TAS2R38 was found to be significantly associated with recurrence, with nonfunctional variants linked to poorer outcomes.

IV. Discussion

In this meta-analysis of 17 studies on outcomes after ESS for CRS, we found that both clinical and genetic signals track with recurrence. Two keep showing up—again and again—as the most reliable: asthma and NSAID intolerance (AERD/NERD), which behave as strong, consistent predictors. Allergy and higher LMSs follow behind—still statistically significant—whereas peripheral blood eosinophil counts never quite deliver a dependable association in the pooled results. On the genetic side, TAS2R38 matters, though more tentatively. Nonfunctional variants were linked to worse surgical outcomes, particularly when contrasted with functional genotypes, but the evidence base is thinner. Our bias checks (funnel plots plus Egger test) suggested low risk for allergy and NSAID intolerance; by contrast, we saw hints of small-study effects for asthma, eosinophils, LMS, and TAS2R38. Put together, clinical comorbidities and genetic background both shape prognosis after ESS—just not with equal certainty.

The forest plots largely back the idea that several clinical factors track with recurrence after ESS. Asthma shows a solid association (OR=2.87), though the heterogeneity is chunky (I^2=61.79%)—different patient mixes, different designs, you can feel it. Allergy is significant too (OR=1.78) with only moderate spread (I^2=34.66%), which reads as a steadier signal. By contrast, NSAID intolerance (AERD/NERD) is the heavyweight here: the biggest pooled effect (OR=4.25) and essentially no heterogeneity (I^2=0%), remarkably consistent across cohorts. Radiology tells a murkier story. Higher LMS relates to recurrence (OR=1.88), but the heterogeneity is sky-high (I^2=92.17%), so study-level quirks likely tug the estimate around. Although eosinophils demonstrated borderline effect sizes that did not reach significance (OR=1.25) and carry substantial heterogeneity (I^2=65.83%), definitions and measurements of "eosinophilia" clearly weren't aligned. Finally, TAS2R38 polymorphism shows a significant link (OR=3.61) with low-to-moderate heterogeneity (I^2=24.27%), hinting that this receptor matters for outcomes—though, honestly, bigger, well-phenotyped cohorts should test that again. The genetic data were based on a relatively small number of studies (k=4), and it remains possible that bias is relevant and needs to be replicated in more studies using larger and multi-ethnic cohorts. Although funnel plots suggested some visual symmetry, Egger test detected small-study effects for asthma, LMS, and eosinophils, which may limit certainty.

A few overlapping mechanisms probably sit behind these links between clinical factors and postsurgical outcomes in CRS. Asthma keeps turning up as a driver of recurrence—no surprise—because type-2 inflammatory circuits, eosinophil-heavy tissue, and airway remodeling span both the upper and lower tracts, which ends up shortening the durability of surgery[19,22,23]. NSAID intolerance, meanwhile, reflects a system-wide wobble in arachidonic-acid metabolism with excess leukotrienes—prime conditions for smoldering inflammation and fast polyp regrowth even after a technically tidy ESS[24,25]. Allergy adds fuel through IgE-mediated cascades that swell the mucosa, loosen the epithelial barrier, and make recurrent polyposis more likely, though its predictive punch isn't uniform across studies[26]. And peripheral/tissue eosinophilia? It often rides along with higher recurrence risk, tracking the more aggressive IL-5– and type-2-skewed CRS endotypes[27]. Higher LMS indicates an increased radiological burden that may act as a surrogate of disease severity or burden and explains its association with surgical failure rates[28,29]. In addition to these predictors for the clinical course, genetic predisposition has been offered as a factor. Polymorphisms of the TAS2R38 bitter taste receptor are thought to alter sinonasal innate immunity through both the modulation of NO production and bacterial clearance. Those with nonfunctional alleles exhibit impaired mucosal defense that translates to worse outcomes and increased recurrence after ESS[14]. That said, not every study sees the same link. Yılmaz et al.[10], in a Turkish cohort, found no meaningful differences across TAS2R38 genotypes—no signal in genotype distribution, no extra bump in postoperative SNOT-22 improvement, and no clear gap in recurrence rates. They did note a faint trend toward more bacterial proliferation in AVI/AVI carriers, but it didn't cross the usual thresholds. Why the mismatch? Sample size is one easy suspect, but population genetics, clinical management, and follow-up length (and loss to follow-up) can each nudge results in different directions. All of which argues for larger, multi-center, multi-ethnic cohorts with standardized phenotyping and longer observation to pin down the true prognostic weight of TAS2R38 in CRS.

Overall, these findings suggest that systemic comorbidities and local sinonasal immune mechanisms interact to influence the long-term prognosis of CRS following surgery. Understanding which predictors may allow clinicians to better tailor peroperative care as well as the intensity of follow-up.

In addition to the clinical and genetic predictors that were pooled in our quantitative analysis, several other factors were assessed across the reference studies. Age was reported in some cohorts as a determinant of higher recurrence risk[20,30], although this finding was not consistent across all populations. Sex and smoking status were often studied, but did not reveal consistent and significant associations with surgical outcomes[22,31]. Occupational exposures and prior sinus surgery were evaluated as well in individual studies. However, the effects were also inconsistent and heterogenous[5,31]. Although rare comorbidities, such as eosinophilic granulomatosis with polyangiitis (EGPA), were suggested to be strong predictors for isolated cohorts, they were not generalizable to the general CRS population[20]. More recently, molecular markers including IL-5 expression, periostin, and type-2 inflammation profiles have been related to disease severity and poor postoperative quality of life[32]. although the evidence is still preliminary and largely limited to translational studies. Taken together, these factors could not be incorporated into our meta-analysis because of insufficient quantitative data, inconsistency in reporting, and lack of study power, underscoring the need for further large-scale research to clarify their prognostic significance.

1. Clinical implications

There are a number of important clinical implications from these findings of this meta-analysis. The identification of asthma and NSAID intolerance suggested as a potential predictor highlights the importance of systemic screening for lower airway co-morbidities and drug hypersensitivity, especially in patients with CRS undergoing ESS. It is likely that patients with these risk factors can be expected to be under closer surveillance postoperatively (for example, possibly considering postoperative follow-up from a pulmonary standpoint only). Possible intervention(s) could be through extended medical therapy, and we would suggest multidisciplinary management with pulmonologists and allergists. The associations with allergy and higher LMS further support the value of preoperative stratifying patients based not only on atopic status but also on radiological severity, which can assist clinicians in predicting disease recurrence and help define future follow-up strategies.

The effect estimates for eosinophils were borderline (P=0.052) and did not achieve statistical significance. The association of TAS2R38 genetic polymorphisms with surgical outcomes suggests emerging evidence for genetic biomarkers in identifying prognostic ability. While there has yet to be a drive toward genetic testing, we can take steps toward Individualised treatment informed by family history as well as immunology that will support their post-operative care. TAS2R38 findings were based on only four studies and rated as low certainty of evidence according to GRADE. For these predictors, our results are best viewed as hypothesis-generating. The observed heterogeneity may partly arise from variations in CRS phenotype, outcome definitions, and follow-up duration. Future large-scale, stratified studies are needed to confirm these associations.

In summary, our results suggest that combining clinical comorbidities, radiological scoring, and genetics in a preoperative assessment could allow for improved risk stratified assessment, and ultimately improve individually planned treatment, resource allocation, and therefore reduce revision surgery in CRS.

There are some limitations to this meta-analysis that should be acknowledged. There were 17 studies included; however, the number of available datasets was limited for some individual predictors, and some factors, such as peripheral eosinophils, LMS, and TAS2R38 polymorphisms, were examined in a fairly limited number of studies, which decreased the precision of pooled estimates. Second, there was considerable heterogeneity across studies in terms of patient selection (CRSwNP vs. CRSsNP), outcome definitions (endoscopic recurrence, radiological scores, or need for revision surgery), and follow-up duration, all of which may have influenced the consistency of results. Third, not all potential predictors were consistently reported with sufficient quantitative data; factors such as age, sex, smoking status, previous sinus surgery, occupational exposures, EGPA, and molecular biomarkers (e.g., IL-5, periostin, T2-high profiles) were evaluated in some cohorts but could not be incorporated into the pooled analysis. Fourth, publication bias could not be excluded, as indicated by Egger test for asthma, eosinophils, and LMSs, although visual inspection of funnel plots suggested mixed results for certain predictors. While there was considerable heterogeneity for asthma, eosinophils, and LMS, we were unable to perform meaningful subgroup analyses or meta-regression due to the limited number of studies per predictor and the incomplete reporting of phenotype-specific or outcome-specific data. For example, individual studies tended to either combine CRSwNP and CRSsNP populations or report different outcome measures as a heterogeneous measure, without stratification. Although sensitivity analyses excluding lower-quality studies did not change the results in a meaningful

way, residual heterogeneity presents an important limitation. Although exploratory meta-regression by follow-up duration was attempted, the number of studies per predictor was insufficient, and the analysis was underpowered (P>0.1).

A further limitation concerns the statistical treatment of data in individual studies. In Adappa et al.[14], ORs could not be directly calculated due to zero cells in the 2×2 tables; therefore, the Haldane–Anscombe correction was applied, and we estimated the OR and CI, which should be considered approximate. In Adappa et al.[15], only mean±standard deviation values of SNOT-22 scores were available, and pooled effect estimates were derived under the assumption of a normal distribution using Z-scores; thus, the reported effect sizes are indirect estimates. In addition, subgroup analyses stratified by CRS phenotype (CRSwNP vs. CRSsNP) could not be performed, as several studies included mixed populations but did not report phenotype-specific outcomes with sufficient statistical detail. Finally, differences in surgical techniques, extent of ESS, and postoperative medical regimens were not uniformly reported, which may have acted as unmeasured confounders.

V. Conclusion

This meta-analysis has shown that asthma and NSAID sensitivity are the most consistent clinical predictors of recurrence after ESS for CRS, and also identifies the contribution of allergy and higher LMS. Peripheral eosinophils were not consistently relevant across studies. Also noted was the association of TAS2R38 genetic variation with poorer outcomes, indicating a role for host genetics in prognosis. Overall, our findings emphasize the need to include clinical comorbidities, radiographic assessment, and genetic markers in the multicomponent preoperative risk stratification approach in order to optimize postoperative care. Large, multi-ethnic, and well-controlled future studies are necessary to substantiate the identified predictors and examine personalized management strategies to minimize recurrence rates in CRS.

ORCID

Abbas Ardalan, *https://orcid.org/0000-0002-7223-9905*
Sahar Adl, *https://orcid.org/0000-0002-5001-3577*
Kosar Moarefvand, *https://orcid.org/0009-0004-0264-0551*
Elham Amirkhani, *https://orcid.org/0009-0001-8503-4212*
Sepehr Faridazar, *https://orcid.org/0009-0007-2838-4228*
Massoud Houshmand, *https://orcid.org/0009-0009-4319-0186*

Authors' Contributions

A.A., S.A., K.M., and M.H. participated in data collection and writing the manuscript. M.H., E.A., A.A., S.A., and S.F. participated in the study design and performed the statistical analysis. M.H., K.M. participated in the study design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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Ethics Approval and Consent to Participate

This study did not require ethical approval, as it only used previously published data. However, all procedures were conducted in accordance with the principles of the Declaration of Helsinki.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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