Clinical predictors of polyps recurring in patients with chronic rhinosinusitis and nasal polyps: a systematic review and meta-analysis*

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Abstract

Background: Identification of perioperative risk factors for recurrent nasal polyps (RNPs) is important for selection of further treatment and determination of appropriate follow-up period. However, the relative prognostic significance of these risk factors has not been investigated.

Methodology: We compared the nasal symptoms, endoscopic polyp and Lund-Mackey computed tomography scores, and the laboratory and pathological findings of RNP and non-RNP patients. The risk of bias was assessed using the Newcastle-Ottawa scale.

Results: Patients with poor nasal symptom scores and olfactory dysfunctions and high Lund-Mackey computed tomography scores were at higher risk of postoperative RNPs, as were those with allergic conditions and elevated tissue and serum eosinophil levels. The tissue neutrophil counts/percentages were significantly lower in the RNP than the other group. The tissue eosinophil level was of higher diagnostic utility than the serum eosinophil level. The RNP diagnostic odds ratio afforded by the tissue eosinophil count or percentage was 54.1247. The area under the receiver operating characteristic curve was 0.936. The sensitivity and specificity were 0.8809 and 0.8834, respectively.

Conclusion: The tissue eosinophil level reliably predicts RNP after endoscopic sinus surgery.

Key words: eosinophils, sinusitis, hypersensitivity, nasal polyps, recurrence

Introduction

Chronic rhinosinusitis (CRS) imposes significant socioeconomic burdens worldwide, affecting 5 to 15% of all subjects in the United States and Europe[1, 2]. In the United States, the healthcare costs range from $6.9 to $9.9 billion a year[3]. Clinically, CRS is divided into CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRScNP)[1]. Over the past several years, several patient-specific treatments have been proposed[4]. However, in many countries, it remains difficult to use cytokine levels to customize CRSwNP patient treatment; this is not cost-effective. Various protocols suggest that, regardless of the endotype, endoscopic sinus surgery (ESS) should be considered for patients who do not improve even after maximal medical treatment[1, 2]. ESS physically removes nasal polyps, ensures sinus ventilation, and restores mucociliary drainage[1]. For recalcitrant CRSwNP, ESS is still considered the gold standard[1, 2]. However, despite the initial improvements, the polyp recurrence rate can attain 60%, and 15-20% of patients require revision surgery[5]. As a result, studies on recurrent nasal polyps (RNPs) after ESS have been conducted. Sinonasal tissue or blood eosinophilia, eosinophil cationic protein, preoperative Lund-Mackey computed tomography (CT) scores, and presence of comorbid asthma have been reported as predictors for recurrence risk[6-10]. Nevertheless, the investigation of the relative prognostic significance of these

factors has not been adequately undertaken. Identification of perioperative risk factors for RNPs would greatly aid selection of further treatments and the choice of appropriate follow-up periods. Therefore, in this meta-analysis, we identify clinical predictors of postoperative RNPs in CRSwNP patients and evaluate the diagnostic utilities of independently associated factors.

Materials and methods

Study protocol and registration

This systematic review and meta-analysis adhered to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[11]. The protocol was prospectively registered in the Open Science Framework (https://osf.io/gq7hu/).

Literature search

We searched the PubMed, SCOPUS, Embase, Web of Science, and Cochrane Central Register of Controlled Trials databases to February 2023. The Mesh terms were: Nasal Polyps, Rhinitis, Sinusitis, Chronic Disease, and Recurrence. The details are shown in Supplementary Table 1. Two authors (JSH and GK) independently reviewed and selected studies via review of titles, abstracts, and texts; any disagreement was resolved via discussion with a third reviewer (MAB).

Selection criteria

The subjects included patients with CRSwNPs that recurred after surgery and who then underwent clinical, laboratory, pathological, or imaging evaluation. Case reports, review articles, those evaluating other nasal diseases, non-English-language articles, and reports lacking data that allowed of statistical analysis, were excluded. We compared the clinical, laboratory, pathological, and imaging data of RNP and non-RNP groups and present standardized mean differences (SMDs) or odds ratios (ORs). The selection strategy is summarized in Figure 1.

Data organization and quality assessment

We used a standard form[12-14] to record patient number, gender, nationality, the tests used to evaluate RNP status, and comorbidities. The p-values of differences between the outcomes of RNP and non-RNP patients were calculated. We compared the percentages and absolute numbers of tissue and serum eosinophils; endoscopic polyp and nasal symptom scores; olfactory function; Lund-Mackey CT scores; and allergic rhinitis, asthma, eosinophilic CRS, aspirin-intolerance, and tissue and serum eosinophilia status[7, 9, 15-45]. Diagnostic accuracy, sensitivity, specificity, and the diagnostic odds ratio (DOR) were calculated; summary receiver operating characteristic (SROC) curves were drawn and areas under the curves (AUCs) calculated; these yielded the true-positive, true-negative, false-positive, and false-negative values. The risk of bias was assessed using the Newcastle-Ottawa scale. The Newcastle-Ottawa Scale is a validated

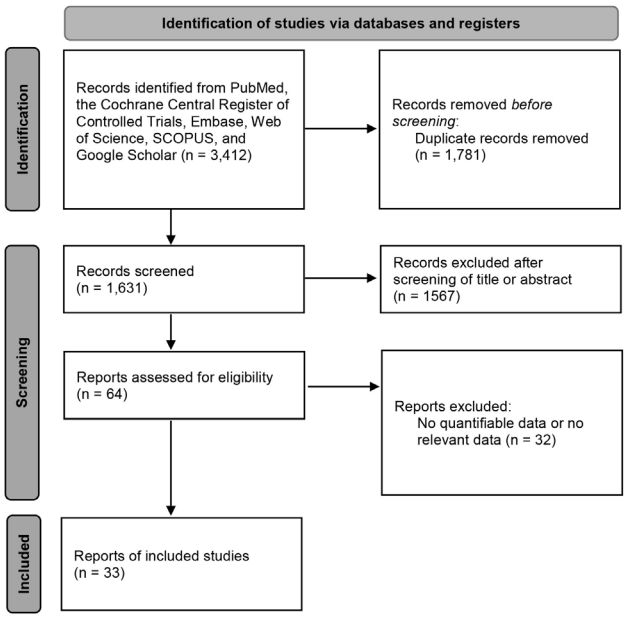


Figure 1. Flow diagram of article selection.

instrument comprising 8 items distributed across three domains, namely selection, comparability, and outcome. This scale was employed to evaluate the quality of the studies incorporated in the analysis. Each item, except for comparability, carries a single point, whereas comparability has the potential to contribute up to two points. Consequently, the total score ranges from 0 to 9, whereby studies are categorized as poor quality if they score between 0 and 2, fair quality if they score between 3 and 5, and good/high quality if they score between 6 and 9[46].

Statistical analyses

R ver. 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses. For continuous variables, the data are the standard mean differences (SMDs). As no standardized methods for evaluation of the eosinophil or neutrophil percentages or absolute counts, the CT score, subjective olfactory dysfunction, or the endoscopic NP or nasal symptom scores are yet available, effect sizes were calculated using the SMDs. Other variables were compared using the odds ratios (ORs) of outcome incidences. The DORs were the (true-positive/false-positive)/(false-negative/true-negative) ratios calculated using a random-effects model and are presented with 95% confidence intervals (CIs). DOR values range from 0 to infinity; higher values indicate better diagnostic performance. A value of 1 is neutral in terms of disease presence/absence; values from 0 to 1 indicate that diagnostic performance is poor. A better SROC curve approaches the upper left corner where the sensitivity and specificity are both 100% (thus 1), indicating optimal diagnostic power. The AUC, thus the area under the SROC curve, ranges from 0 to 1. The closer the AUC to 1, the better the diagnostic utility.

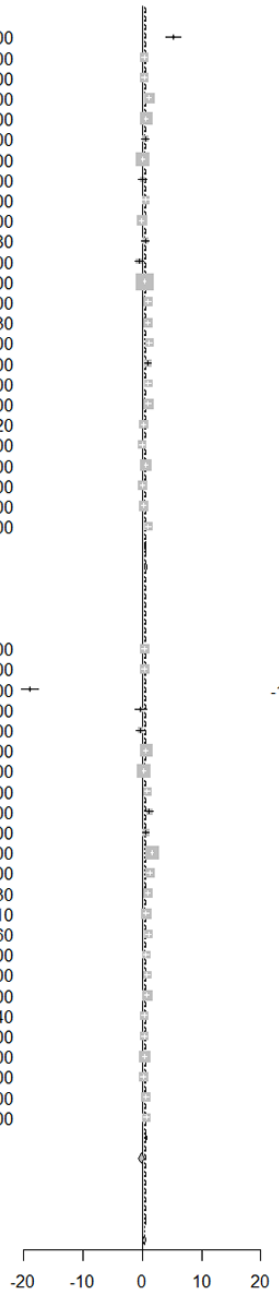
The I^2 test was used to assess heterogeneity. This examines among-study variability. The I^2 score ranges from 0 to 100; higher values indicate more heterogeneity. If significant heterogeneity was evident ($I^2 > 50$), the meta-analysis employed the DerSimonian-Laird random-effects model. Otherwise ($I^2 < 50$), a fixed-effects model was used. All p-values are two-tailed. We performed sensitivity analyses to evaluate the effects of individual studies on the overall results. The funnel plot and the Egger test were used to detect publication bias. If such bias was suspected, the funnel plot asymmetry was corrected and confirmed employing the trim-and-fill method. In addition, a meta-regression analysis was performed to examine the potential association between the follow-up periods and the laboratory, clinical, and pathological features, as well as the underlying comorbidities, in the recurrent CRSwNP. If such an association was observed, a subgroup analysis was subsequently conducted.

Results

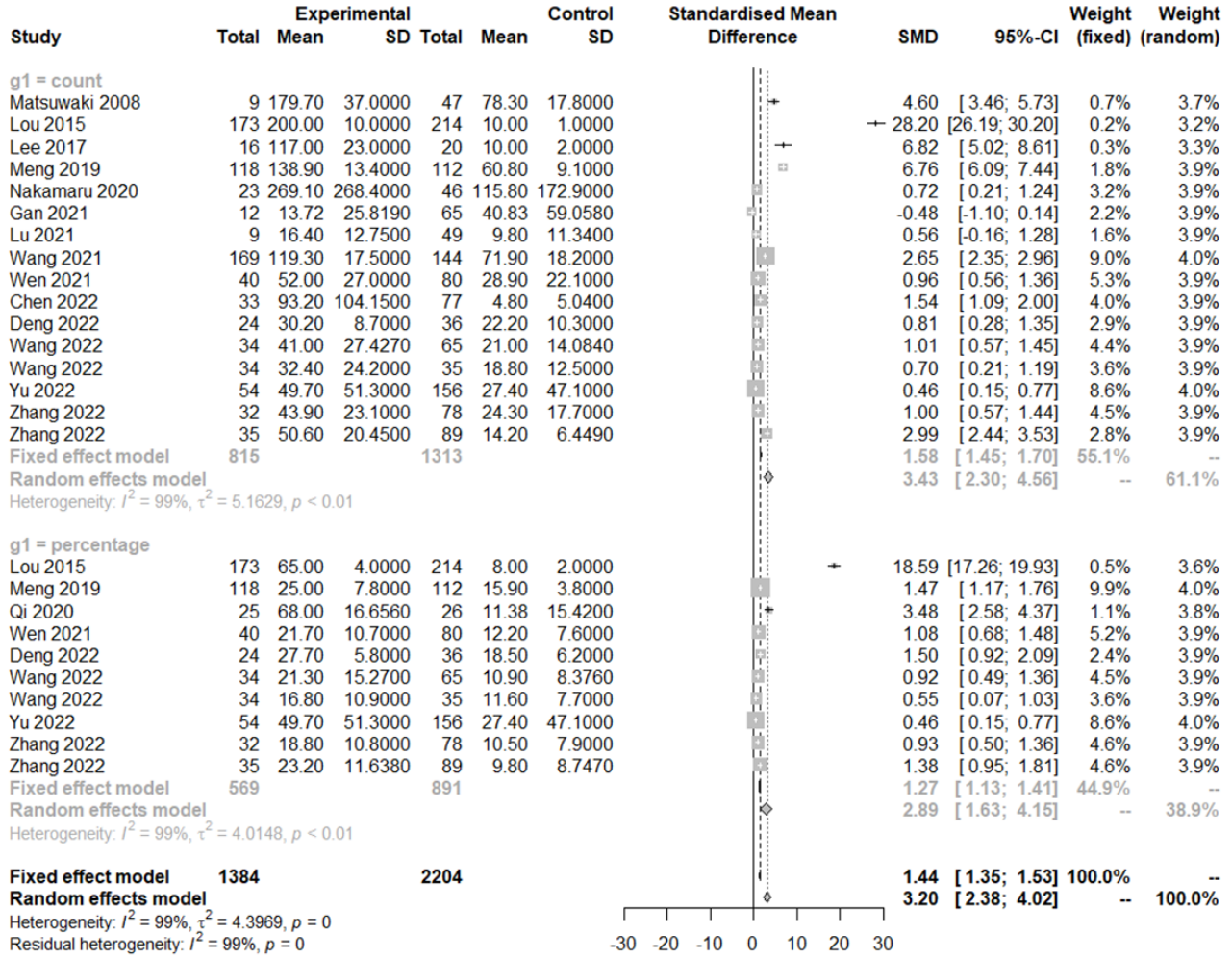
A total of 4,516 patients enrolled in 33 studies were finally included. The study characteristics and bias assessments are

Figure 2A

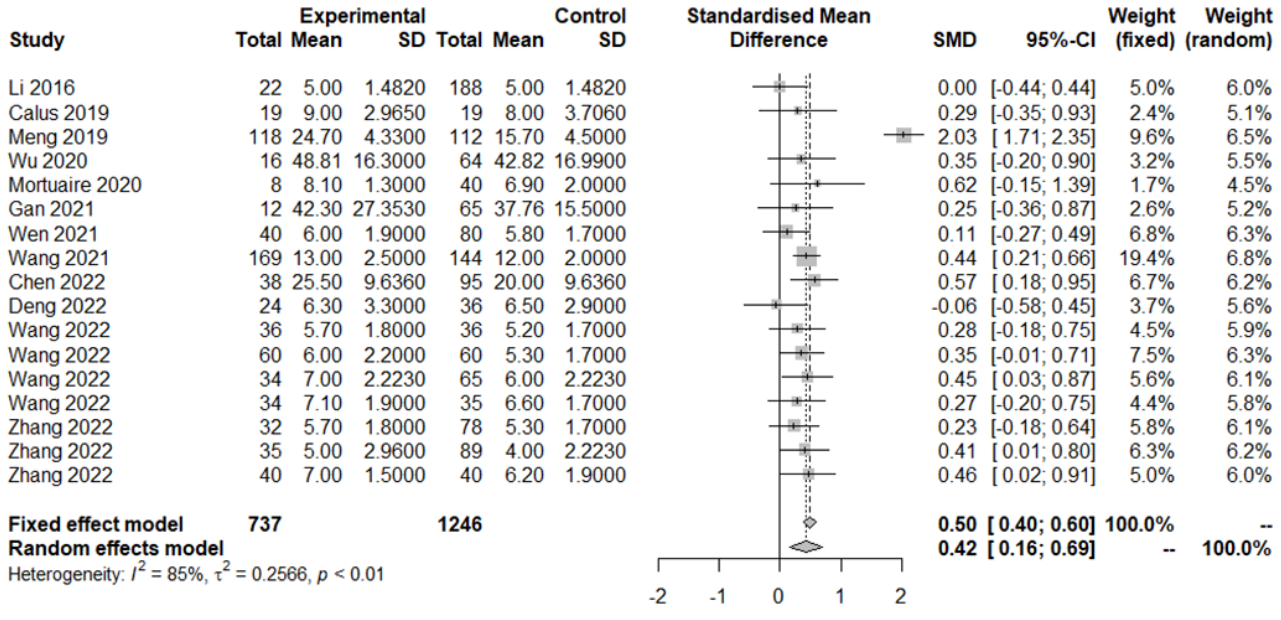
Study	Experimental Total	Experimental Mean	Experimental SD	Control Total	Control Mean	Control SD	SMD	95%-CI	Weight (fixed)	Weight (random)
g1 = count										
Matsuwaki 2008	9	577.80	113.5000	47	269.70	40.9000	5.26	[4.02; 6.50]	0.2%	1.5%
Brescia 2015	24	0.33	0.1800	155	0.27	0.1900	0.32	[-0.11; 0.75]	1.8%	2.1%
Brescia 2015	24	0.33	0.1800	155	0.27	0.1900	0.32	[-0.11; 0.75]	1.8%	2.1%
Yenigun 2015	80	6.60	0.9000	78	5.50	1.0000	1.15	[0.81; 1.49]	2.9%	2.1%
Brescia 2017	57	0.47	0.5200	223	0.28	0.2000	0.64	[0.35; 0.94]	3.8%	2.1%
Lee 2017	16	0.35	0.1900	20	0.21	0.3200	0.51	[-0.16; 1.18]	0.7%	1.9%
Meng 2019	118	0.50	1.3000	112	0.40	2.2000	0.06	[-0.20; 0.31]	4.9%	2.2%
Mortuaire 2020	8	662.00	574.0000	40	652.00	180.0000	0.04	[-0.72; 0.79]	0.6%	1.9%
Nakamaru 2020	23	552.10	288.4000	46	327.50	432.8000	0.57	[0.06; 1.08]	1.3%	2.0%
Salvador 2020	45	0.38	0.2500	87	0.40	0.3100	-0.07	[-0.43; 0.29]	2.5%	2.1%
Gan 2021	12	0.40	0.2816	65	0.31	0.1480	0.51	[-0.11; 1.13]	0.9%	2.0%
Lu 2021	9	31.80	131.8000	49	102.60	118.0100	-0.58	[-1.30; 0.14]	0.6%	1.9%
Peng 2021	142	501.70	103.3000	249	457.00	112.6000	0.41	[0.20; 0.62]	7.6%	2.2%
Wen 2021	40	0.40	0.1000	80	0.30	0.1000	0.99	[0.59; 1.39]	2.1%	2.1%
Chen 2022	38	0.40	0.3110	95	0.19	0.1630	0.97	[0.58; 1.36]	2.1%	2.1%
Chen 2022	33	0.42	0.2660	77	0.18	0.1700	1.17	[0.74; 1.61]	1.7%	2.1%
Deng 2022	24	200.00	120.0000	36	100.00	100.0000	0.91	[0.37; 1.45]	1.1%	2.0%
Wang 2022	36	0.30	0.1000	36	0.20	0.1000	0.99	[0.50; 1.48]	1.4%	2.1%
Wang 2022	60	0.30	0.1000	60	0.20	0.1000	0.99	[0.61; 1.37]	2.3%	2.1%
Wang 2022	34	241.10	144.8480	65	218.50	103.6320	0.19	[-0.23; 0.60]	1.9%	2.1%
Wang 2022	34	0.30	0.1000	35	0.30	0.1000	0.00	[-0.47; 0.47]	1.5%	2.1%
Yu 2022	54	360.40	265.3000	156	232.40	173.0000	0.64	[0.32; 0.95]	3.3%	2.1%
Zhang 2022	32	0.30	0.1000	78	0.30	0.1000	0.00	[-0.41; 0.41]	2.0%	2.1%
Zhang 2022	35	296.90	108.9000	89	272.50	119.0000	0.21	[-0.18; 0.60]	2.2%	2.1%
Zhang 2022	40	0.30	0.1000	40	0.20	0.1000	0.99	[0.52; 1.46]	1.5%	2.1%
Fixed effect model	1027			2173			0.52	[0.45; 0.60]	52.7%	--
Random effects model							0.60	[0.39; 0.81]	--	51.1%
Heterogeneity: I^2 = 85%, τ^2 = 0.2316, p < 0.01										
g1 = percentage										
Brescia 2015	24	4.92	2.8000	155	3.97	2.5300	0.37	[-0.06; 0.80]	1.8%	2.1%
Brescia 2015	24	4.92	2.8000	155	3.97	2.5300	0.37	[-0.06; 0.80]	1.8%	2.1%
Lou 2015	173	4.00	0.2000	214	7.80	0.2000	-18.96	[-20.32; -17.61]	0.2%	1.4%
Nakayama 2016	5	6.80	4.4000	19	8.40	6.4000	-0.25	[-1.24; 0.73]	0.3%	1.7%
Nakayama 2016	12	6.80	3.6000	19	8.40	6.4000	-0.28	[-1.01; 0.44]	0.6%	1.9%
Brescia 2017	57	6.20	4.8000	223	4.20	2.9600	0.58	[0.29; 0.88]	3.8%	2.1%
Meng 2019	118	7.40	3.3000	112	6.60	4.0000	0.22	[-0.04; 0.48]	4.9%	2.2%
Du 2020	28	8.06	4.9660	68	4.90	3.6300	0.77	[0.32; 1.23]	1.6%	2.1%
Qi 2020	25	6.96	3.0300	26	3.69	2.4200	1.18	[0.58; 1.78]	0.9%	2.0%
Wu 2020	16	4.88	3.2000	64	3.06	3.0100	0.59	[0.04; 1.15]	1.1%	2.0%
Wang 2021	169	8.70	2.2000	144	4.90	2.4000	1.65	[1.39; 1.91]	5.0%	2.2%
Wen 2021	40	4.20	1.2000	80	2.90	1.0000	1.21	[0.80; 1.62]	2.0%	2.1%
Wu 2021	68	6.25	3.3950	40	3.35	2.9130	0.89	[0.48; 1.30]	2.0%	2.1%
Chen 2022	38	5.51	5.3960	95	3.14	2.6310	0.65	[0.26; 1.03]	2.2%	2.1%
Chen 2022	33	6.00	3.9280	77	2.50	3.0760	1.04	[0.61; 1.47]	1.8%	2.1%
Deng 2022	24	3.00	1.0000	36	2.30	1.1000	0.65	[0.12; 1.18]	1.2%	2.0%
Wang 2022	36	5.10	2.1000	36	3.60	1.6000	0.79	[0.31; 1.28]	1.4%	2.1%
Wang 2022	60	4.90	2.2000	60	3.40	1.5000	0.79	[0.42; 1.16]	2.4%	2.1%
Wang 2022	34	3.40	1.5560	65	2.90	1.7040	0.30	[-0.12; 0.72]	1.9%	2.1%
Wang 2022	34	5.40	2.6000	35	4.70	1.8000	0.31	[-0.16; 0.79]	1.5%	2.1%
Yu 2022	54	4.60	3.5000	156	3.60	2.5000	0.36	[0.05; 0.67]	3.4%	2.1%
Zhang 2022	32	3.60	1.3000	78	3.40	1.3000	0.15	[-0.26; 0.56]	1.9%	2.1%
Zhang 2022	35	3.50	1.4000	89	2.70	1.2000	0.63	[0.23; 1.03]	2.1%	2.1%
Zhang 2022	40	3.30	1.0000	40	2.60	1.0000	0.69	[0.24; 1.15]	1.6%	2.1%
Fixed effect model	1179			2086			0.60	[0.51; 0.68]	47.3%	--
Random effects model							-0.06	[-0.60; 0.47]	--	48.9%
Heterogeneity: I^2 = 97%, τ^2 = 1.7123, p < 0.01										
Fixed effect model	**2206**			**4259**			**0.56**	**[0.50; 0.62]**	**100.0%**	**--**
Random effects model							**0.34**	**[0.07; 0.62]**	**--**	**100.0%**
Heterogeneity: I^2 = 96%, τ^2 = 0.9061, p < 0.01										
Residual heterogeneity: I^2 = 96%, p < 0.01										



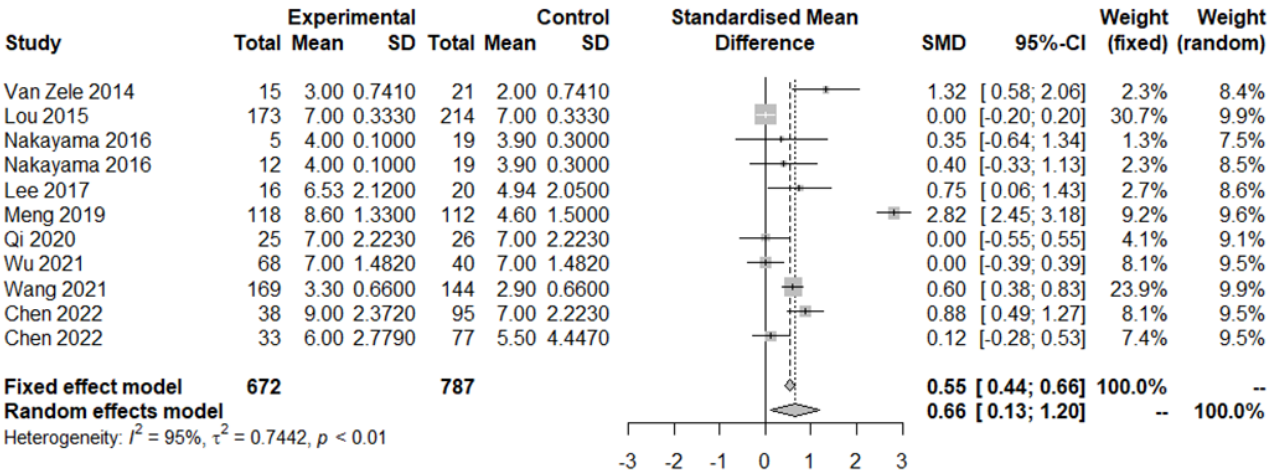
2B


Study
Experimental Total Mean SD
Control Total Mean SD
Standardised Mean Difference
SMD 95%-CI
Weight (fixed) Weight (random)
g1 = count
Matsuwaki 2008 9 179.70 37.0000 47 78.30 17.8000 4.60 [3.46; 5.73] 0.7% 3.7%
Lou 2015 173 200.00 10.0000 214 10.00 1.0000 28.20 [26.19; 30.20] 0.2% 3.2%
Lee 2017 16 117.00 23.0000 20 10.00 2.0000 6.82 [5.02; 8.61] 0.3% 3.3%
Meng 2019 118 138.90 13.4000 112 60.80 9.1000 6.76 [6.09; 7.44] 1.8% 3.9%
Nakamaru 2020 23 269.10 268.4000 46 115.80 172.9000 0.72 [0.21; 1.24] 3.2% 3.9%
Gan 2021 12 13.72 25.8190 65 40.83 59.0580 -0.48 [-1.10; 0.14] 2.2% 3.9%
Lu 2021 9 16.40 12.7500 49 9.80 11.3400 0.56 [-0.16; 1.28] 1.6% 3.9%
Wang 2021 169 119.30 17.5000 144 71.90 18.2000 2.65 [2.35; 2.96] 9.0% 4.0%
Wen 2021 40 52.00 27.0000 80 28.90 22.1000 0.96 [0.56; 1.36] 5.3% 3.9%
Chen 2022 33 93.20 104.1500 77 4.80 5.0400 1.54 [1.09; 2.00] 4.0% 3.9%
Deng 2022 24 30.20 8.7000 36 22.20 10.3000 0.81 [0.28; 1.35] 2.9% 3.9%
Wang 2022 34 41.00 27.4270 65 21.00 14.0840 1.01 [0.57; 1.45] 4.4% 3.9%
Wang 2022 34 32.40 24.2000 35 18.80 12.5000 0.70 [0.21; 1.19] 3.6% 3.9%
Yu 2022 54 49.70 51.3000 156 27.40 47.1000 0.46 [0.15; 0.77] 8.6% 4.0%
Zhang 2022 32 43.90 23.1000 78 24.30 17.7000 1.00 [0.57; 1.44] 4.5% 3.9%
Zhang 2022 35 50.60 20.4500 89 14.20 6.4490 2.99 [2.44; 3.53] 2.8% 3.9%
Fixed effect model 815 1313 1.58 [1.45; 1.70] 55.1% --
Random effects model 3.43 [2.30; 4.56] -- 61.1%
Heterogeneity: I^2 = 99%, τ^2 = 5.1629, p < 0.01
g1 = percentage
Lou 2015 173 65.00 4.0000 214 8.00 2.0000 18.59 [17.26; 19.93] 0.5% 3.6%
Meng 2019 118 25.00 7.8000 112 15.90 3.8000 1.47 [1.17; 1.76] 9.9% 4.0%
Qi 2020 25 68.00 16.6560 26 11.38 15.4200 3.48 [2.58; 4.37] 1.1% 3.8%
Wen 2021 40 21.70 10.7000 80 12.20 7.6000 1.08 [0.68; 1.48] 5.2% 3.9%
Deng 2022 24 27.70 5.8000 36 18.50 6.2000 1.50 [0.92; 2.09] 2.4% 3.9%
Wang 2022 34 21.30 15.2700 65 10.90 8.3760 0.92 [0.49; 1.36] 4.5% 3.9%
Wang 2022 34 16.80 10.9000 35 11.60 7.7000 0.55 [0.07; 1.03] 3.6% 3.9%
Yu 2022 54 49.70 51.3000 156 27.40 47.1000 0.46 [0.15; 0.77] 8.6% 4.0%
Zhang 2022 32 18.80 10.8000 78 10.50 7.9000 0.93 [0.50; 1.36] 4.6% 3.9%
Zhang 2022 35 23.20 11.6380 89 9.80 8.7470 1.38 [0.95; 1.81] 4.6% 3.9%
Fixed effect model 569 891 1.27 [1.13; 1.41] 44.9% --
Random effects model 2.89 [1.63; 4.15] -- 38.9%
Heterogeneity: I^2 = 99%, τ^2 = 4.0148, p < 0.01
Fixed effect model 1384 2204 1.44 [1.35; 1.53] 100.0% --
Random effects model 3.20 [2.38; 4.02] -- 100.0%
Heterogeneity: I^2 = 99%, τ^2 = 4.3969, p = 0
Residual heterogeneity: I^2 = 99%, p = 0
-30 -20 -10 0 10 20 30

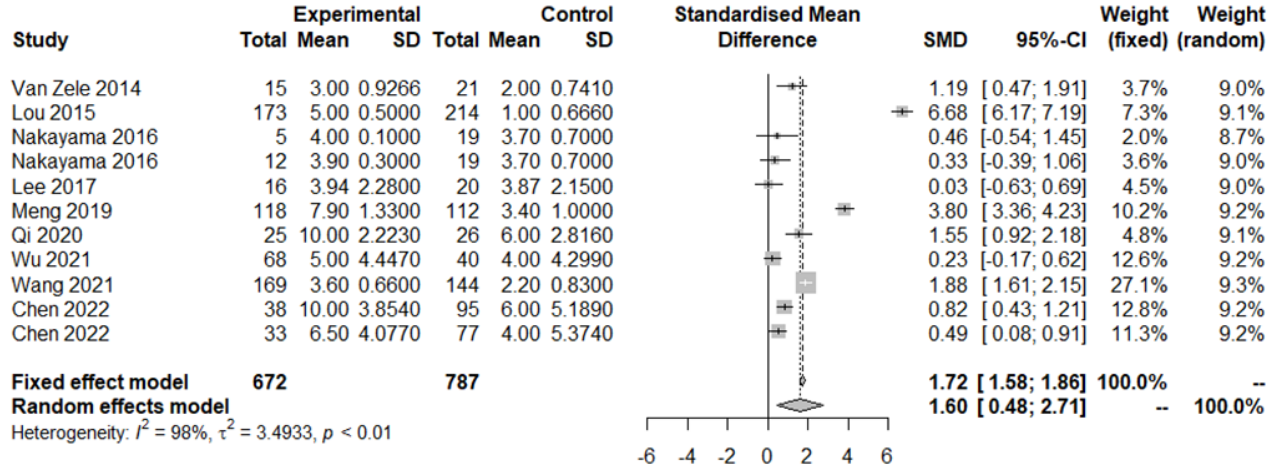
2C


Study
Experimental Total Mean SD
Control Total Mean SD
Standardised Mean Difference
SMD 95%-CI
Weight (fixed) Weight (random)
Li 2016 22 5.00 1.4820 188 5.00 1.4820 0.00 [-0.44; 0.44] 5.0% 6.0%
Calus 2019 19 9.00 2.9650 19 8.00 3.7060 0.29 [-0.35; 0.93] 2.4% 5.1%
Meng 2019 118 24.70 4.3300 112 15.70 4.5000 2.03 [1.71; 2.35] 9.6% 6.5%
Wu 2020 16 48.81 16.3000 64 42.82 16.9900 0.35 [-0.20; 0.90] 3.2% 5.5%
Mortuaire 2020 8 8.10 1.3000 40 6.90 2.0000 0.62 [-0.15; 1.39] 1.7% 4.5%
Gan 2021 12 42.30 27.3530 65 37.76 15.5000 0.25 [-0.36; 0.87] 2.6% 5.2%
Wen 2021 40 6.00 1.9000 80 5.80 1.7000 0.11 [-0.27; 0.49] 6.8% 6.3%
Wang 2021 169 13.00 2.5000 144 12.00 2.0000 0.44 [0.21; 0.66] 19.4% 6.8%
Chen 2022 38 25.50 9.6360 95 20.00 9.6360 0.57 [0.18; 0.95] 6.7% 6.2%
Deng 2022 24 6.30 3.3000 36 6.50 2.9000 -0.06 [-0.58; 0.45] 3.7% 5.6%
Wang 2022 36 5.70 1.8000 36 5.20 1.7000 0.28 [-0.18; 0.75] 4.5% 5.9%
Wang 2022 60 6.00 2.2000 60 5.30 1.7000 0.35 [-0.01; 0.71] 7.5% 6.3%
Wang 2022 34 7.00 2.2230 65 6.00 2.2230 0.45 [0.03; 0.87] 5.6% 6.1%
Wang 2022 34 7.10 1.9000 35 6.60 1.7000 0.27 [-0.20; 0.75] 4.4% 5.8%
Zhang 2022 32 5.70 1.8000 78 5.30 1.7000 0.23 [-0.18; 0.64] 5.8% 6.1%
Zhang 2022 35 5.00 2.9600 89 4.00 2.2230 0.41 [0.01; 0.80] 6.3% 6.2%
Zhang 2022 40 7.00 1.5000 40 6.20 1.9000 0.46 [0.02; 0.91] 5.0% 6.0%
Fixed effect model 737 1246 0.50 [0.40; 0.60] 100.0% --
Random effects model 0.42 [0.16; 0.69] -- 100.0%
Heterogeneity: I^2 = 85%, τ^2 = 0.2566, p < 0.01
-2 -1 0 1 2

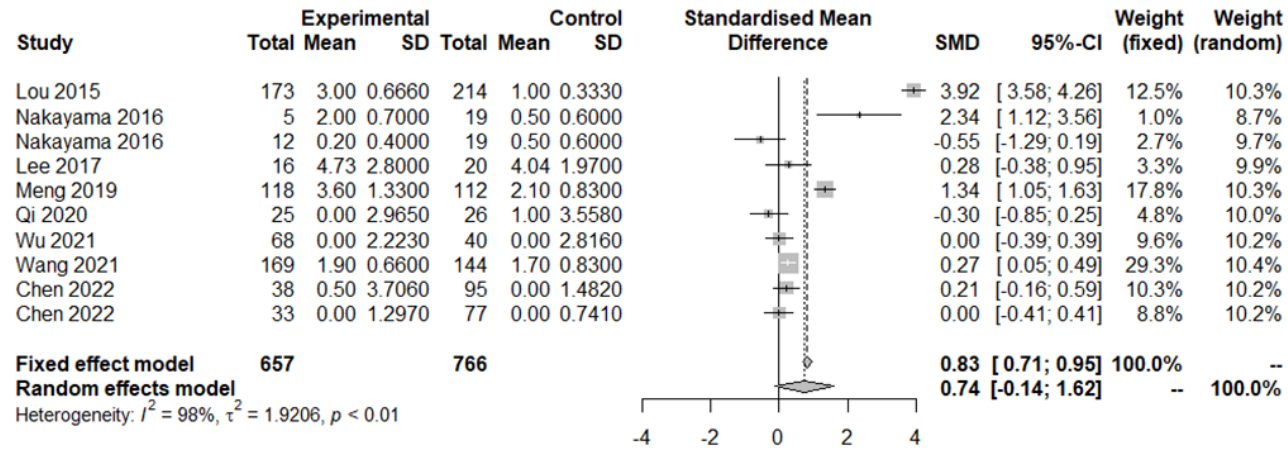
2D


Study | Experimental Total Mean SD | Control Total Mean SD | Standardised Mean Difference | SMD 95%-CI | Weight (fixed) | Weight (random)
Van Zele 2014 15 3.00 0.7410 21 2.00 0.7410 1.32 [0.58; 2.06] 2.3% 8.4%
Lou 2015 173 7.00 0.3330 214 7.00 0.3330 0.00 [-0.20; 0.20] 30.7% 9.9%
Nakayama 2016 5 4.00 0.1000 19 3.90 0.3000 0.35 [-0.64; 1.34] 1.3% 7.5%
Nakayama 2016 12 4.00 0.1000 19 3.90 0.3000 0.40 [-0.33; 1.13] 2.3% 8.5%
Lee 2017 16 6.53 2.1200 20 4.94 2.0500 0.75 [0.06; 1.43] 2.7% 8.6%
Meng 2019 118 8.60 1.3300 112 4.60 1.5000 2.82 [2.45; 3.18] 9.2% 9.6%
Qi 2020 25 7.00 2.2230 26 7.00 2.2230 0.00 [-0.55; 0.55] 4.1% 9.1%
Wu 2021 68 7.00 1.4820 40 7.00 1.4820 0.00 [-0.39; 0.39] 8.1% 9.5%
Wang 2021 169 3.30 0.6600 144 2.90 0.6600 0.60 [0.38; 0.83] 23.9% 9.9%
Chen 2022 38 9.00 2.3720 95 7.00 2.2230 0.88 [0.49; 1.27] 8.1% 9.5%
Chen 2022 33 6.00 2.7790 77 5.50 4.4470 0.12 [-0.28; 0.53] 7.4% 9.5%
Fixed effect model 672 787 0.55 [0.44; 0.66] 100.0% --
Random effects model 0.66 [0.13; 1.20] -- 100.0%
Heterogeneity: I^2 = 95%, τ^2 = 0.7442, p < 0.01
-3 -2 -1 0 1 2 3

2E


Study | Experimental Total Mean SD | Control Total Mean SD | Standardised Mean Difference | SMD 95%-CI | Weight (fixed) | Weight (random)
Van Zele 2014 15 3.00 0.9266 21 2.00 0.7410 1.19 [0.47; 1.91] 3.7% 9.0%
Lou 2015 173 5.00 0.5000 214 1.00 0.6660 6.68 [6.17; 7.19] 7.3% 9.1%
Nakayama 2016 5 4.00 0.1000 19 3.70 0.7000 0.46 [-0.54; 1.45] 2.0% 8.7%
Nakayama 2016 12 3.90 0.3000 19 3.70 0.7000 0.33 [-0.39; 1.06] 3.6% 9.0%
Lee 2017 16 3.94 2.2800 20 3.87 2.1500 0.03 [-0.63; 0.69] 4.5% 9.0%
Meng 2019 118 7.90 1.3300 112 3.40 1.0000 3.80 [3.36; 4.23] 10.2% 9.2%
Qi 2020 25 10.00 2.2230 26 6.00 2.8160 1.55 [0.92; 2.18] 4.8% 9.1%
Wu 2021 68 5.00 4.4470 40 4.00 4.2990 0.23 [-0.17; 0.62] 12.6% 9.2%
Wang 2021 169 3.60 0.6600 144 2.20 0.8300 1.88 [1.61; 2.15] 27.1% 9.3%
Chen 2022 38 10.00 3.8540 95 6.00 5.1890 0.82 [0.43; 1.21] 12.8% 9.2%
Chen 2022 33 6.50 4.0770 77 4.00 5.3740 0.49 [0.08; 0.91] 11.3% 9.2%
Fixed effect model 672 787 1.72 [1.58; 1.86] 100.0% --
Random effects model 1.60 [0.48; 2.71] -- 100.0%
Heterogeneity: I^2 = 98%, τ^2 = 3.4933, p < 0.01
-6 -4 -2 0 2 4 6

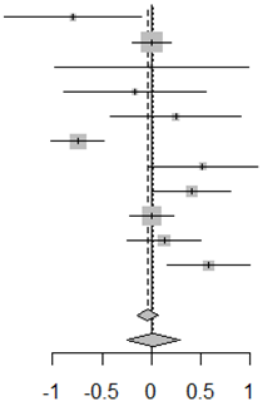
2F


Study | Experimental Total Mean SD | Control Total Mean SD | Standardised Mean Difference | SMD 95%-CI | Weight (fixed) | Weight (random)
Lou 2015 173 3.00 0.6660 214 1.00 0.3330 3.92 [3.58; 4.26] 12.5% 10.3%
Nakayama 2016 5 2.00 0.7000 19 0.50 0.6000 2.34 [1.12; 3.56] 1.0% 8.7%
Nakayama 2016 12 0.20 0.4000 19 0.50 0.6000 -0.55 [-1.29; 0.19] 2.7% 9.7%
Lee 2017 16 4.73 2.8000 20 4.04 1.9700 0.28 [-0.38; 0.95] 3.3% 9.9%
Meng 2019 118 3.60 1.3300 112 2.10 0.8300 1.34 [1.05; 1.63] 17.8% 10.3%
Qi 2020 25 0.00 2.9650 26 1.00 3.5580 -0.30 [-0.85; 0.25] 4.8% 10.0%
Wu 2021 68 0.00 2.2230 40 0.00 2.8160 0.00 [-0.39; 0.39] 9.6% 10.2%
Wang 2021 169 1.90 0.6600 144 1.70 0.8300 0.27 [0.05; 0.49] 29.3% 10.4%
Chen 2022 38 0.50 3.7060 95 0.00 1.4820 0.21 [-0.16; 0.59] 10.3% 10.2%
Chen 2022 33 0.00 1.2970 77 0.00 0.7410 0.00 [-0.41; 0.41] 8.8% 10.2%
Fixed effect model 657 766 0.83 [0.71; 0.95] 100.0% --
Random effects model 0.74 [-0.14; 1.62] -- 100.0%
Heterogeneity: I^2 = 98%, τ^2 = 1.9206, p < 0.01
-4 -2 0 2 4

2G

Study	Experimental Total	Mean	SD	Control Total	Mean	SD	SMD	95%-CI	Weight (fixed)	Weight (random)
Van Zele 2014	15	0.50	0.3700	21	1.00	0.7410	-0.79	[-1.48; -0.10]	2.4%	7.0%
Lou 2015	173	6.00	0.1666	214	6.00	0.1666	0.00	[-0.20; 0.20]	28.0%	12.1%
Nakayama 2016	5	2.40	0.9000	19	2.40	0.5000	0.00	[-0.99; 0.99]	1.2%	4.7%
Nakayama 2016	12	2.30	0.7000	19	2.40	0.5000	-0.17	[-0.89; 0.56]	2.1%	6.7%
Lee 2017	16	5.28	2.2400	20	4.74	2.0800	0.25	[-0.41; 0.91]	2.6%	7.3%
Meng 2019	118	4.60	1.1600	112	5.60	1.5000	-0.75	[-1.01; -0.48]	15.7%	11.5%
Qi 2020	25	5.00	1.4820	26	4.00	2.2230	0.52	[-0.04; 1.08]	3.6%	8.3%
Wu 2021	68	6.00	2.2230	40	5.00	2.8160	0.40	[0.01; 0.80]	7.2%	10.2%
Wang 2021	169	2.10	0.8300	144	2.10	0.8300	0.00	[-0.22; 0.22]	22.8%	12.0%
Chen 2022	38	5.50	4.4470	95	5.00	3.7060	0.13	[-0.25; 0.50]	7.9%	10.4%
Chen 2022	33	5.00	4.0770	77	3.00	3.1500	0.58	[0.16; 0.99]	6.5%	9.9%
Fixed effect model	**672**			**787**			**-0.04**	**[-0.14; 0.07]**	**100.0%**	--
Random effects model							**0.02**	**[-0.25; 0.29]**	--	**100.0%**

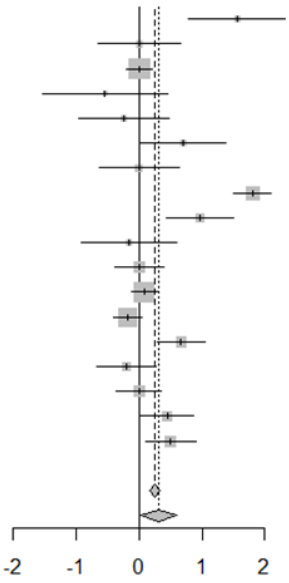
Heterogeneity: I^2 = 80%, τ^2 = 0.1429, p < 0.01



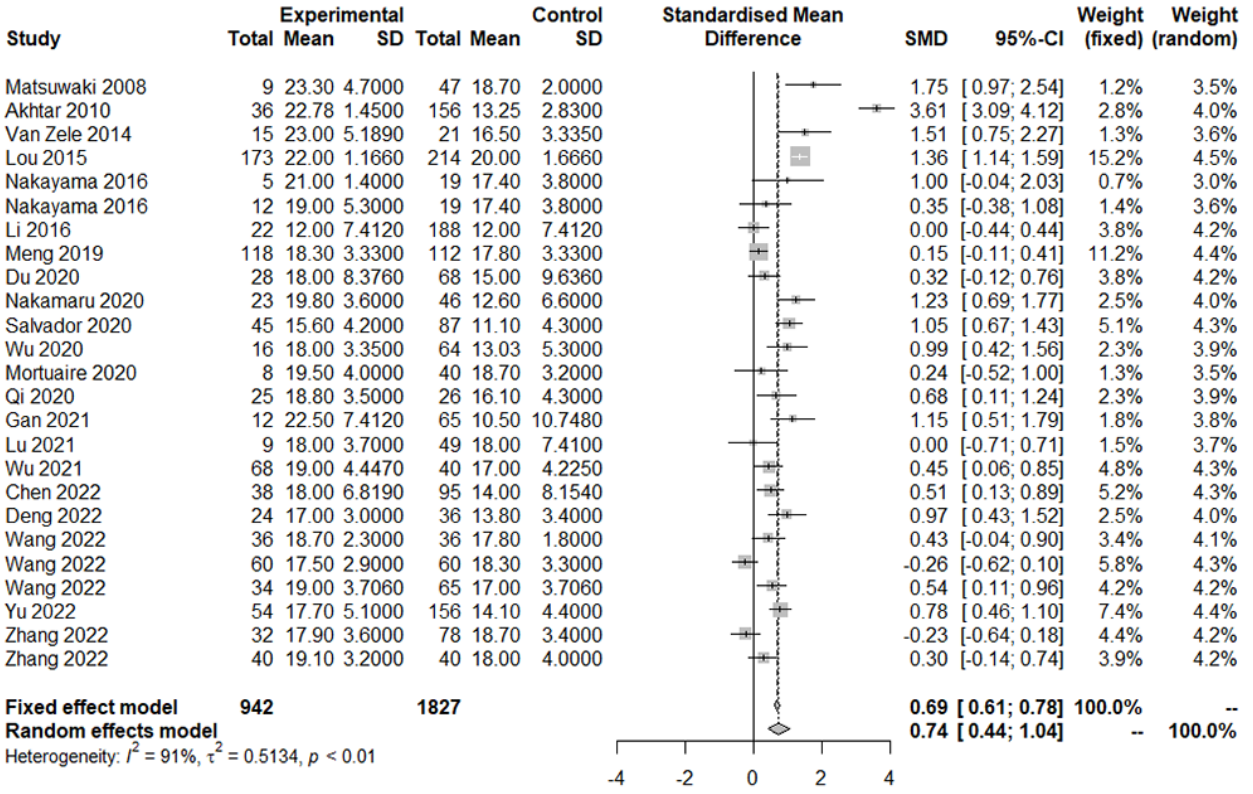
2H

Study	Experimental Total	Mean	SD	Control Total	Mean	SD	SMD	95%-CI	Weight (fixed)	Weight (random)
Matsuwaki 2008	9	0.89	0.1100	47	0.78	0.0600	1.56	[0.78; 2.33]	1.2%	4.5%
Van Zele 2014	15	5.00	1.1110	21	5.00	2.2230	0.00	[-0.66; 0.66]	1.7%	5.0%
Lou 2015	173	5.00	0.1666	214	5.00	0.1666	0.00	[-0.20; 0.20]	18.6%	6.6%
Nakayama 2016	5	4.40	0.9000	19	5.20	1.5000	-0.55	[-1.55; 0.45]	0.7%	3.7%
Nakayama 2016	12	4.80	1.8000	19	5.20	1.5000	-0.24	[-0.97; 0.49]	1.4%	4.7%
Lee 2017	16	6.06	2.0200	20	4.80	1.5400	0.70	[0.02; 1.38]	1.6%	4.9%
Calus 2019	19	4.00	1.4820	19	4.00	1.4820	0.00	[-0.64; 0.64]	1.8%	5.1%
Meng 2019	118	6.40	1.6600	112	3.80	1.1600	1.80	[1.49; 2.11]	7.9%	6.3%
Nakamaru 2020	23	6.00	1.0000	46	4.30	2.0000	0.97	[0.44; 1.50]	2.7%	5.5%
Mortuaire 2020	8	2.20	0.6100	40	2.30	0.5800	-0.17	[-0.93; 0.59]	1.3%	4.6%
Wu 2021	68	5.00	1.4820	40	5.00	1.4820	0.00	[-0.39; 0.39]	4.9%	6.0%
Peng 2021	142	10.30	3.5000	249	10.00	3.7000	0.08	[-0.12; 0.29]	17.6%	6.6%
Wang 2021	169	5.00	1.0000	144	5.20	1.1600	-0.19	[-0.41; 0.04]	15.1%	6.5%
Chen 2022	38	4.00	1.4820	95	3.00	1.4820	0.67	[0.29; 1.06]	5.0%	6.0%
Wang 2022	36	8.50	1.8000	36	8.90	2.1000	-0.20	[-0.67; 0.26]	3.5%	5.8%
Wang 2022	60	9.50	2.2000	60	9.50	2.1000	0.00	[-0.36; 0.36]	5.8%	6.1%
Wang 2022	34	9.00	2.2230	65	8.00	2.2230	0.45	[0.03; 0.87]	4.2%	5.9%
Zhang 2022	35	10.00	2.2230	89	8.00	4.4470	0.50	[0.11; 0.90]	4.8%	6.0%
Fixed effect model	**980**			**1335**			**0.25**	**[0.16; 0.33]**	**100.0%**	--
Random effects model							**0.31**	**[0.02; 0.60]**	--	**100.0%**

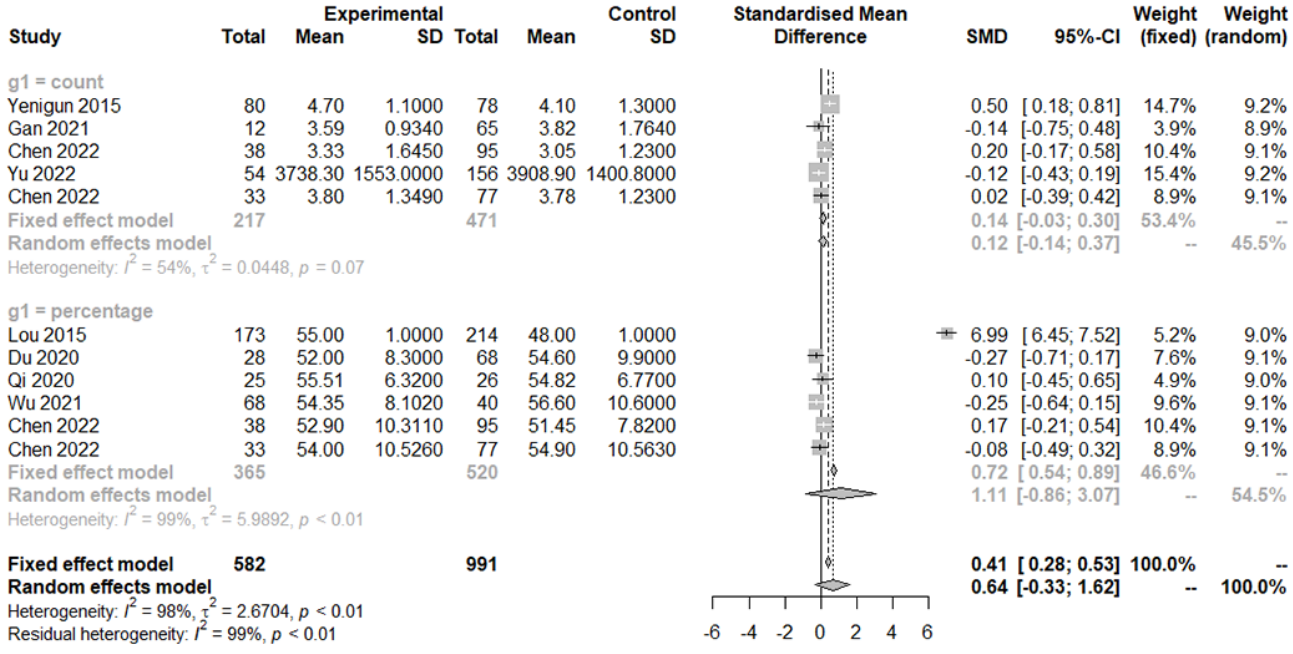
Heterogeneity: I^2 = 89%, τ^2 = 0.3159, p < 0.01



2I


Study | Experimental Total Mean SD | Control Total Mean SD | Standardised Mean Difference | SMD 95%-CI | Weight (fixed) | Weight (random)
Matsuwaki 2008 9 23.30 4.7000 47 18.70 2.0000 1.75 [0.97; 2.54] 1.2% 3.5%
Akhtar 2010 36 22.78 1.4500 156 13.25 2.8300 3.61 [3.09; 4.12] 2.8% 4.0%
Van Zele 2014 15 23.00 5.1890 21 16.50 3.3350 1.51 [0.75; 2.27] 1.3% 3.6%
Lou 2015 173 22.00 1.1660 214 20.00 1.6660 1.36 [1.14; 1.59] 15.2% 4.5%
Nakayama 2016 5 21.00 1.4000 19 17.40 3.8000 1.00 [-0.04; 2.03] 0.7% 3.0%
Nakayama 2016 12 19.00 5.3000 19 17.40 3.8000 0.35 [-0.38; 1.08] 1.4% 3.6%
Li 2016 22 12.00 7.4120 188 12.00 7.4120 0.00 [-0.44; 0.44] 3.8% 4.2%
Meng 2019 118 18.30 3.3300 112 17.80 3.3300 0.15 [-0.11; 0.41] 11.2% 4.4%
Du 2020 28 18.00 8.3760 68 15.00 9.6360 0.32 [-0.12; 0.76] 3.8% 4.2%
Nakamaru 2020 23 19.80 3.6000 46 12.60 6.6000 1.23 [0.69; 1.77] 2.5% 4.0%
Salvador 2020 45 15.60 4.2000 87 11.10 4.3000 1.05 [0.67; 1.43] 5.1% 4.3%
Wu 2020 16 18.00 3.3500 64 13.03 5.3000 0.99 [0.42; 1.56] 2.3% 3.9%
Mortuaire 2020 8 19.50 4.0000 40 18.70 3.2000 0.24 [-0.52; 1.00] 1.3% 3.5%
Qi 2020 25 18.80 3.5000 26 16.10 4.3000 0.68 [0.11; 1.24] 2.3% 3.9%
Gan 2021 12 22.50 7.4120 65 10.50 10.7480 1.15 [0.51; 1.79] 1.8% 3.8%
Lu 2021 9 18.00 3.7000 49 18.00 7.4100 0.00 [-0.71; 0.71] 1.5% 3.7%
Wu 2021 68 19.00 4.4470 40 17.00 4.2250 0.45 [0.06; 0.85] 4.8% 4.3%
Chen 2022 38 18.00 6.8190 95 14.00 8.1540 0.51 [0.13; 0.89] 5.2% 4.3%
Deng 2022 24 17.00 3.0000 36 13.80 3.4000 0.97 [0.43; 1.52] 2.5% 4.0%
Wang 2022 36 18.70 2.3000 36 17.80 1.8000 0.43 [-0.04; 0.90] 3.4% 4.1%
Wang 2022 60 17.50 2.9000 60 18.30 3.3000 -0.26 [-0.62; 0.10] 5.8% 4.3%
Wang 2022 34 19.00 3.7060 65 17.00 3.7060 0.54 [0.11; 0.96] 4.2% 4.2%
Yu 2022 54 17.70 5.1000 156 14.10 4.4000 0.78 [0.46; 1.10] 7.4% 4.4%
Zhang 2022 32 17.90 3.6000 78 18.70 3.4000 -0.23 [-0.64; 0.18] 4.4% 4.2%
Zhang 2022 40 19.10 3.2000 40 18.00 4.0000 0.30 [-0.14; 0.74] 3.9% 4.2%
Fixed effect model 942 1827 0.69 [0.61; 0.78] 100.0% --
Random effects model 0.74 [0.44; 1.04] -- 100.0%
Heterogeneity: I^2 = 91%, τ^2 = 0.5134, p < 0.01
-4 -2 0 2 4

2J


Study | Experimental Total Mean SD | Control Total Mean SD | Standardised Mean Difference | SMD 95%-CI | Weight (fixed) | Weight (random)
g1 = count
Yenigun 2015 80 4.70 1.1000 78 4.10 1.3000 0.50 [0.18; 0.81] 14.7% 9.2%
Gan 2021 12 3.59 0.9340 65 3.82 1.7640 -0.14 [-0.75; 0.48] 3.9% 8.9%
Chen 2022 38 3.33 1.6450 95 3.05 1.2300 0.20 [-0.17; 0.58] 10.4% 9.1%
Yu 2022 54 3738.30 1553.0000 156 3908.90 1400.8000 -0.12 [-0.43; 0.19] 15.4% 9.2%
Chen 2022 33 3.80 1.3490 77 3.78 1.2300 0.02 [-0.39; 0.42] 8.9% 9.1%
Fixed effect model 217 471 0.14 [-0.03; 0.30] 53.4% --
Random effects model 0.12 [-0.14; 0.37] -- 45.5%
Heterogeneity: I^2 = 54%, τ^2 = 0.0448, p = 0.07
g1 = percentage
Lou 2015 173 55.00 1.0000 214 48.00 1.0000 6.99 [6.45; 7.52] 5.2% 9.0%
Du 2020 28 52.00 8.3000 68 54.60 9.9000 -0.27 [-0.71; 0.17] 7.6% 9.1%
Qi 2020 25 55.51 6.3200 26 54.82 6.7700 0.10 [-0.45; 0.65] 4.9% 9.0%
Wu 2021 68 54.35 8.1020 40 56.60 10.6000 -0.25 [-0.64; 0.15] 9.6% 9.1%
Chen 2022 38 52.90 10.3110 95 51.45 7.8200 0.17 [-0.21; 0.54] 10.4% 9.1%
Chen 2022 33 54.00 10.5260 77 54.90 10.5630 -0.08 [-0.49; 0.32] 8.9% 9.1%
Fixed effect model 365 520 0.72 [0.54; 0.89] 46.6% --
Random effects model 1.11 [-0.86; 3.07] -- 54.5%
Heterogeneity: I^2 = 99%, τ^2 = 5.9892, p < 0.01
Fixed effect model 582 991 0.41 [0.28; 0.53] 100.0% --
Random effects model 0.64 [-0.33; 1.62] -- 100.0%
Heterogeneity: I^2 = 98%, τ^2 = 2.6704, p < 0.01
Residual heterogeneity: I^2 = 99%, p < 0.01
-6 -4 -2 0 2 4 6

2K

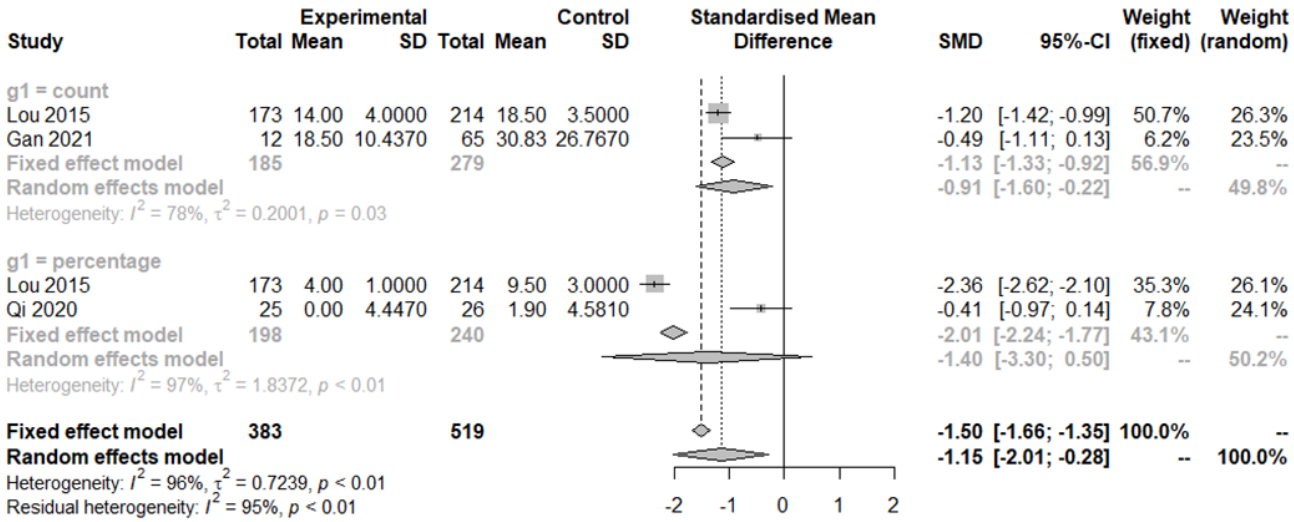
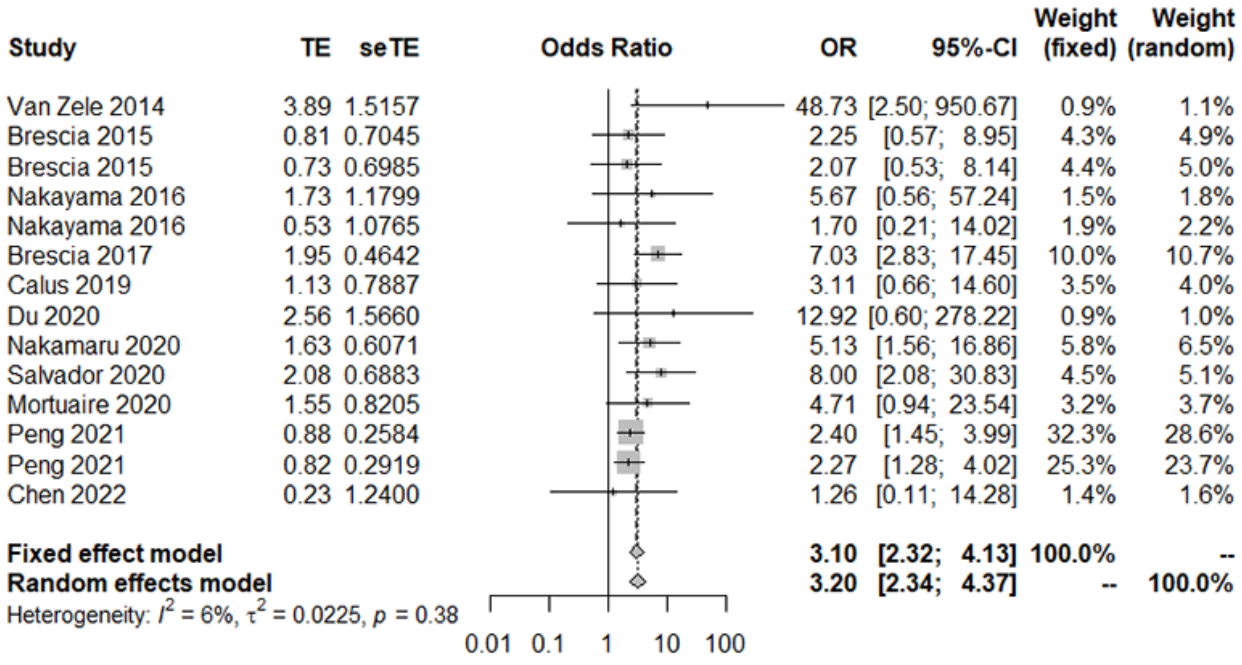
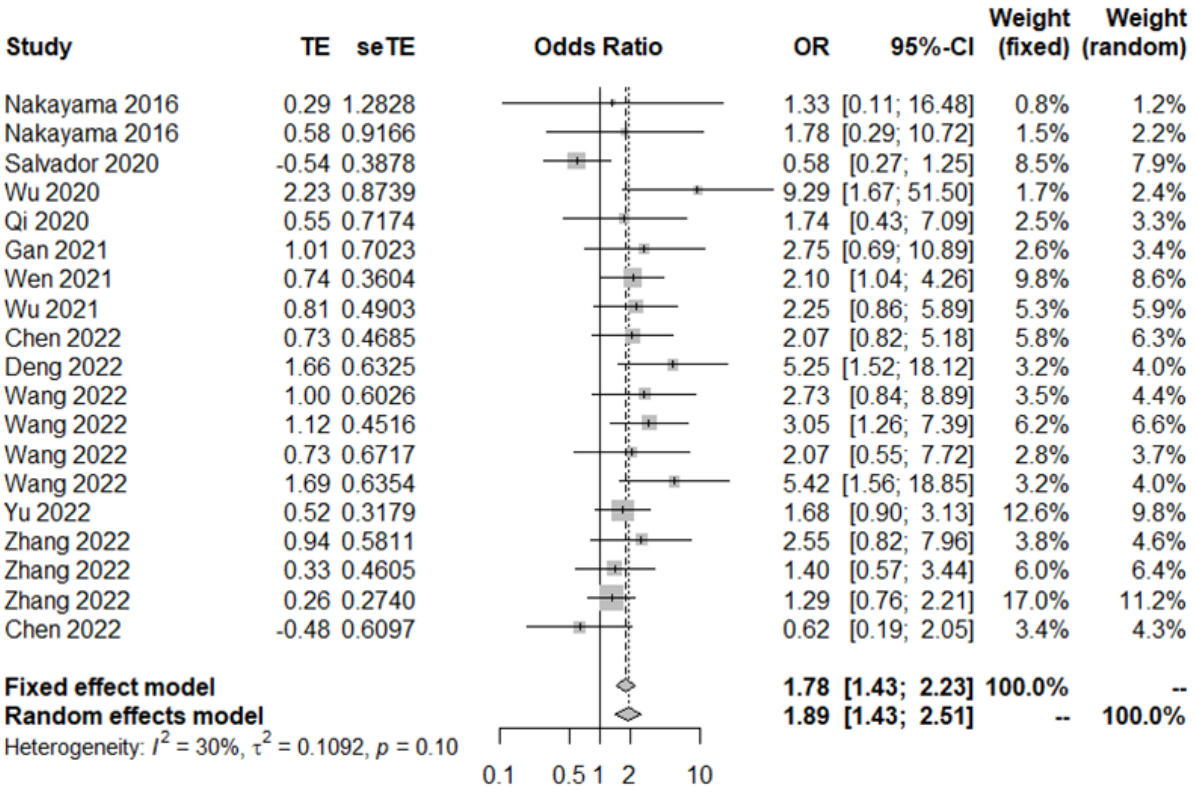


Figure 2. The clinical, laboratory, and pathological features of patients with recurrent and non-recurrent CRSwNP. (A) Blood eosinophil levels, (B) tissue eosinophil levels, (C) total nasal symptom scores, (D) nasal obstruction symptom scores, (E) subjective olfactory dysfunction, (F) facial pain/headache symptom scores, (G) rhinorrhea symptom scores, (H) endoscopic nasal polyp scores, (I) Lund Mackey CT scores, (J) blood neutrophil levels, and (K) tissue neutrophil levels.

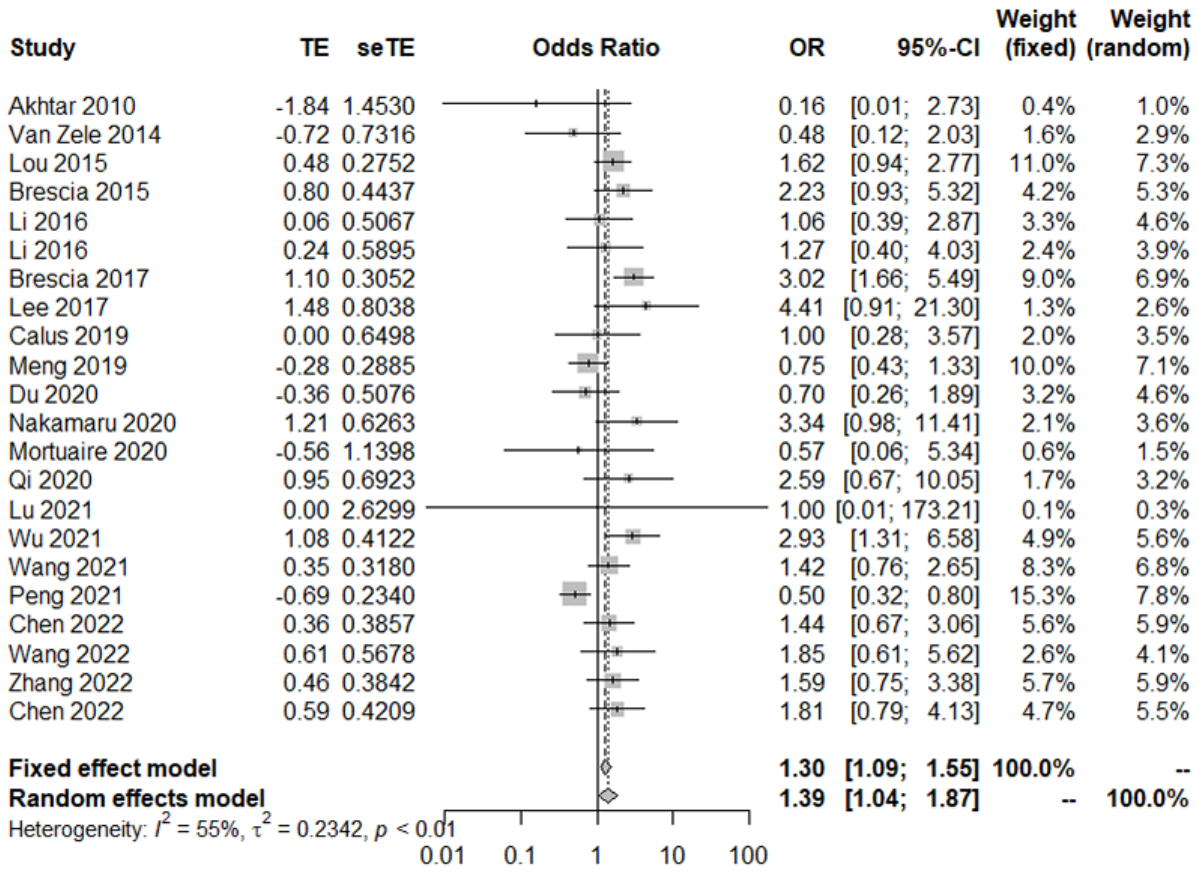
Figure 3A



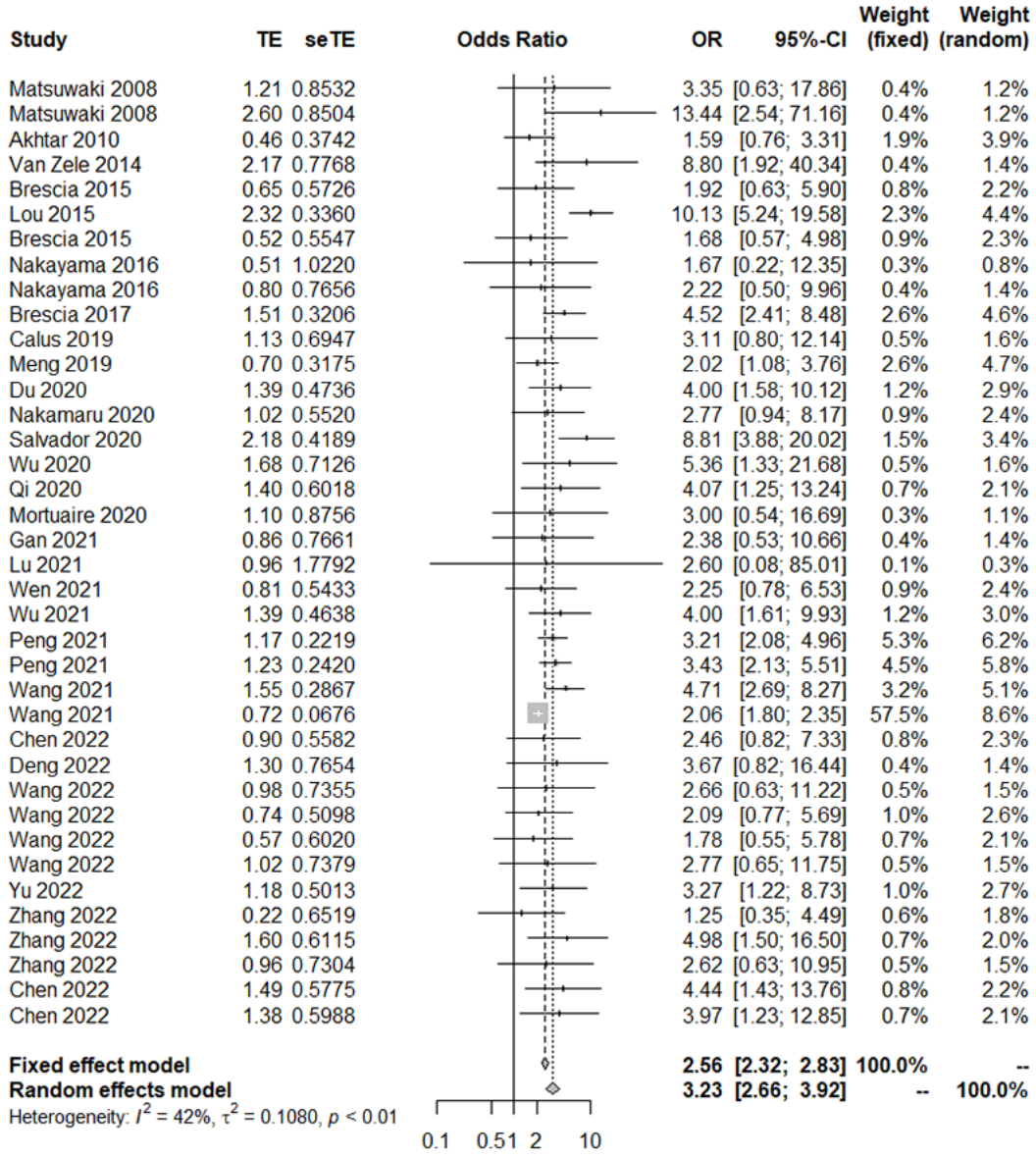
3B


Study TE seTE Odds Ratio OR 95%-CI Weight (fixed) Weight (random)
Nakayama 2016 0.29 1.2828 1.33 [0.11; 16.48] 0.8% 1.2%
Nakayama 2016 0.58 0.9166 1.78 [0.29; 10.72] 1.5% 2.2%
Salvador 2020 -0.54 0.3878 0.58 [0.27; 1.25] 8.5% 7.9%
Wu 2020 2.23 0.8739 9.29 [1.67; 51.50] 1.7% 2.4%
Qi 2020 0.55 0.7174 1.74 [0.43; 7.09] 2.5% 3.3%
Gan 2021 1.01 0.7023 2.75 [0.69; 10.89] 2.6% 3.4%
Wen 2021 0.74 0.3604 2.10 [1.04; 4.26] 9.8% 8.6%
Wu 2021 0.81 0.4903 2.25 [0.86; 5.89] 5.3% 5.9%
Chen 2022 0.73 0.4685 2.07 [0.82; 5.18] 5.8% 6.3%
Deng 2022 1.66 0.6325 5.25 [1.52; 18.12] 3.2% 4.0%
Wang 2022 1.00 0.6026 2.73 [0.84; 8.89] 3.5% 4.4%
Wang 2022 1.12 0.4516 3.05 [1.26; 7.39] 6.2% 6.6%
Wang 2022 0.73 0.6717 2.07 [0.55; 7.72] 2.8% 3.7%
Wang 2022 1.69 0.6354 5.42 [1.56; 18.85] 3.2% 4.0%
Yu 2022 0.52 0.3179 1.68 [0.90; 3.13] 12.6% 9.8%
Zhang 2022 0.94 0.5811 2.55 [0.82; 7.96] 3.8% 4.6%
Zhang 2022 0.33 0.4605 1.40 [0.57; 3.44] 6.0% 6.4%
Zhang 2022 0.26 0.2740 1.29 [0.76; 2.21] 17.0% 11.2%
Chen 2022 -0.48 0.6097 0.62 [0.19; 2.05] 3.4% 4.3%
Fixed effect model 1.78 [1.43; 2.23] 100.0% --
Random effects model 1.89 [1.43; 2.51] -- 100.0%
Heterogeneity: I^2 = 30%, τ^2 = 0.1092, p = 0.10
0.1 0.5 1 2 10

3C


Study TE seTE Odds Ratio OR 95%-CI Weight (fixed) Weight (random)
Akhtar 2010 -1.84 1.4530 0.16 [0.01; 2.73] 0.4% 1.0%
Van Zele 2014 -0.72 0.7316 0.48 [0.12; 2.03] 1.6% 2.9%
Lou 2015 0.48 0.2752 1.62 [0.94; 2.77] 11.0% 7.3%
Brescia 2015 0.80 0.4437 2.23 [0.93; 5.32] 4.2% 5.3%
Li 2016 0.06 0.5067 1.06 [0.39; 2.87] 3.3% 4.6%
Li 2016 0.24 0.5895 1.27 [0.40; 4.03] 2.4% 3.9%
Brescia 2017 1.10 0.3052 3.02 [1.66; 5.49] 9.0% 6.9%
Lee 2017 1.48 0.8038 4.41 [0.91; 21.30] 1.3% 2.6%
Calus 2019 0.00 0.6498 1.00 [0.28; 3.57] 2.0% 3.5%
Meng 2019 -0.28 0.2885 0.75 [0.43; 1.33] 10.0% 7.1%
Du 2020 -0.36 0.5076 0.70 [0.26; 1.89] 3.2% 4.6%
Nakamaru 2020 1.21 0.6263 3.34 [0.98; 11.41] 2.1% 3.6%
Mortuaire 2020 -0.56 1.1398 0.57 [0.06; 5.34] 0.6% 1.5%
Qi 2020 0.95 0.6923 2.59 [0.67; 10.05] 1.7% 3.2%
Lu 2021 0.00 2.6299 1.00 [0.01; 173.21] 0.1% 0.3%
Wu 2021 1.08 0.4122 2.93 [1.31; 6.58] 4.9% 5.6%
Wang 2021 0.35 0.3180 1.42 [0.76; 2.65] 8.3% 6.8%
Peng 2021 -0.69 0.2340 0.50 [0.32; 0.80] 15.3% 7.8%
Chen 2022 0.36 0.3857 1.44 [0.67; 3.06] 5.6% 5.9%
Wang 2022 0.61 0.5678 1.85 [0.61; 5.62] 2.6% 4.1%
Zhang 2022 0.46 0.3842 1.59 [0.75; 3.38] 5.7% 5.9%
Chen 2022 0.59 0.4209 1.81 [0.79; 4.13] 4.7% 5.5%
Fixed effect model 1.30 [1.09; 1.55] 100.0% --
Random effects model 1.39 [1.04; 1.87] -- 100.0%
Heterogeneity: I^2 = 55%, τ^2 = 0.2342, p < 0.01
0.01 0.1 1 10 100

3D



3E

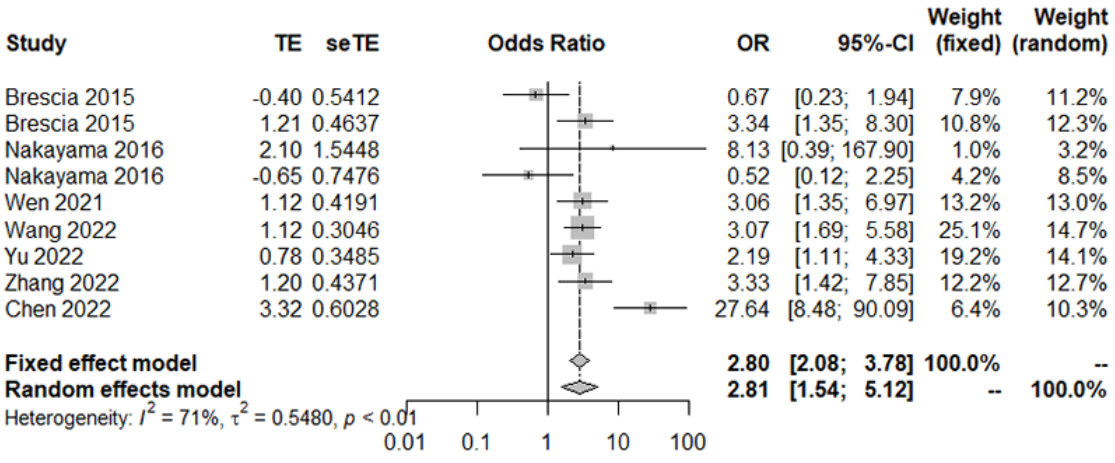
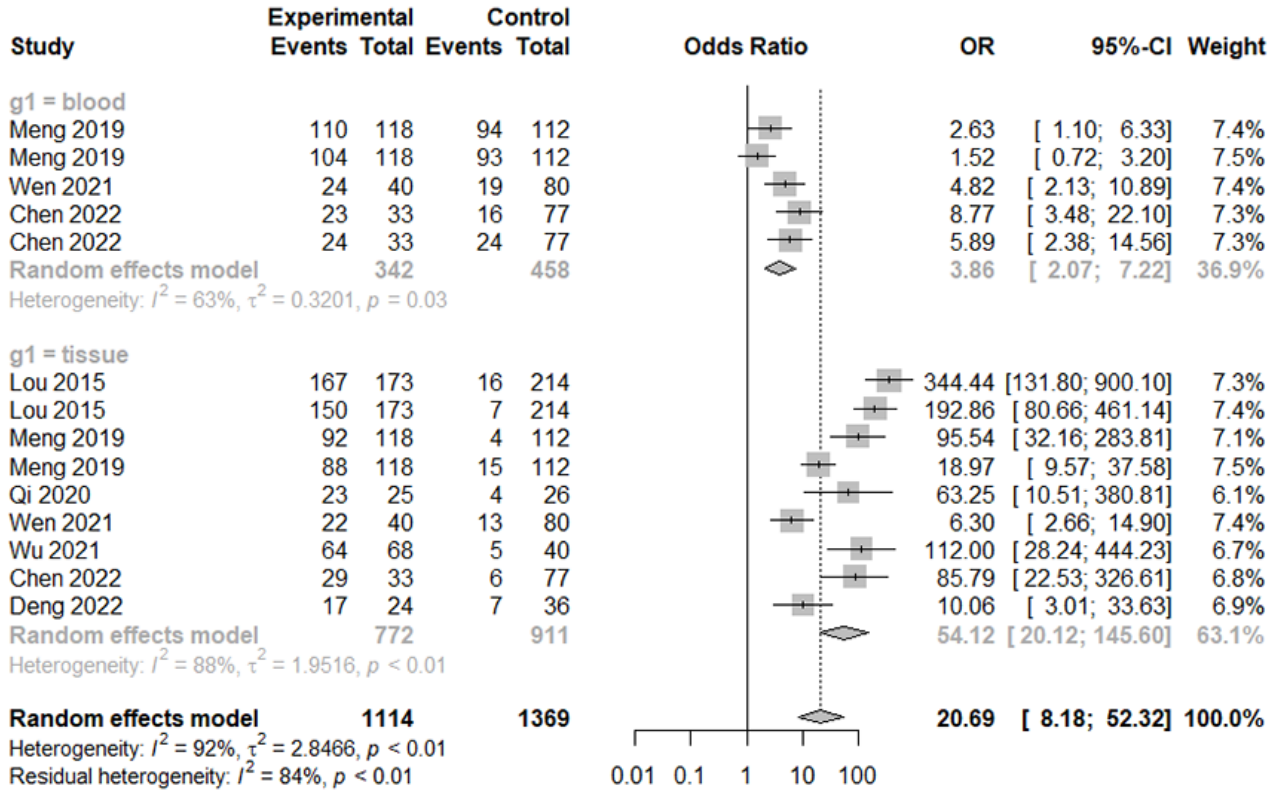
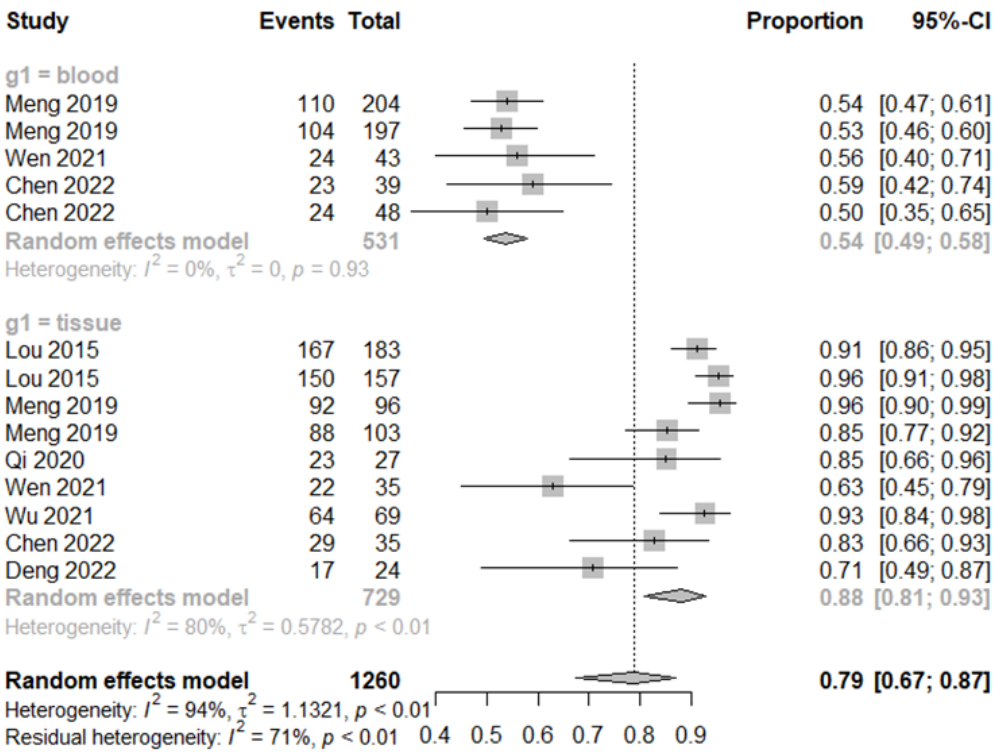


Figure 3. The comorbidities of recurrent CRSwNP and non-recurrent CRSwNP patients Aspirin-intolerance (A), allergic rhinitis (B), atopy (C), asthma (D), and eosinophilic chronic sinusitis (E).

Figure 4A


Study
Experimental Events Total
Control Events Total
Odds Ratio
OR 95%-CI Weight
g1 = blood
Meng 2019 110 118 94 112 2.63 [1.10; 6.33] 7.4%
Meng 2019 104 118 93 112 1.52 [0.72; 3.20] 7.5%
Wen 2021 24 40 19 80 4.82 [2.13; 10.89] 7.4%
Chen 2022 23 33 16 77 8.77 [3.48; 22.10] 7.3%
Chen 2022 24 33 24 77 5.89 [2.38; 14.56] 7.3%
Random effects model 342 458 3.86 [2.07; 7.22] 36.9%
Heterogeneity: I^2 = 63%, τ^2 = 0.3201, p = 0.03
g1 = tissue
Lou 2015 167 173 16 214 344.44 [131.80; 900.10] 7.3%
Lou 2015 150 173 7 214 192.86 [80.66; 461.14] 7.4%
Meng 2019 92 118 4 112 95.54 [32.16; 283.81] 7.1%
Meng 2019 88 118 15 112 18.97 [9.57; 37.58] 7.5%
Qi 2020 23 25 4 26 63.25 [10.51; 380.81] 6.1%
Wen 2021 22 40 13 80 6.30 [2.66; 14.90] 7.4%
Wu 2021 64 68 5 40 112.00 [28.24; 444.23] 6.7%
Chen 2022 29 33 6 77 85.79 [22.53; 326.61] 6.8%
Deng 2022 17 24 7 36 10.06 [3.01; 33.63] 6.9%
Random effects model 772 911 54.12 [20.12; 145.60] 63.1%
Heterogeneity: I^2 = 88%, τ^2 = 1.9516, p < 0.01
Random effects model 1114 1369 20.69 [8.18; 52.32] 100.0%
Heterogeneity: I^2 = 92%, τ^2 = 2.8466, p < 0.01
Residual heterogeneity: I^2 = 84%, p < 0.01
0.01 0.1 1 10 100

4B


Study
Events Total
Proportion 95%-CI
g1 = blood
Meng 2019 110 204 0.54 [0.47; 0.61]
Meng 2019 104 197 0.53 [0.46; 0.60]
Wen 2021 24 43 0.56 [0.40; 0.71]
Chen 2022 23 39 0.59 [0.42; 0.74]
Chen 2022 24 48 0.50 [0.35; 0.65]
Random effects model 531 0.54 [0.49; 0.58]
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.93
g1 = tissue
Lou 2015 167 183 0.91 [0.86; 0.95]
Lou 2015 150 157 0.96 [0.91; 0.98]
Meng 2019 92 96 0.96 [0.90; 0.99]
Meng 2019 88 103 0.85 [0.77; 0.92]
Qi 2020 23 27 0.85 [0.66; 0.96]
Wen 2021 22 35 0.63 [0.45; 0.79]
Wu 2021 64 69 0.93 [0.84; 0.98]
Chen 2022 29 35 0.83 [0.66; 0.93]
Deng 2022 17 24 0.71 [0.49; 0.87]
Random effects model 729 0.88 [0.81; 0.93]
Heterogeneity: I^2 = 80%, τ^2 = 0.5782, p < 0.01
Random effects model 1260 0.79 [0.67; 0.87]
Heterogeneity: I^2 = 94%, τ^2 = 1.1321, p < 0.01
Residual heterogeneity: I^2 = 71%, p < 0.01
0.4 0.5 0.6 0.7 0.8 0.9

4C

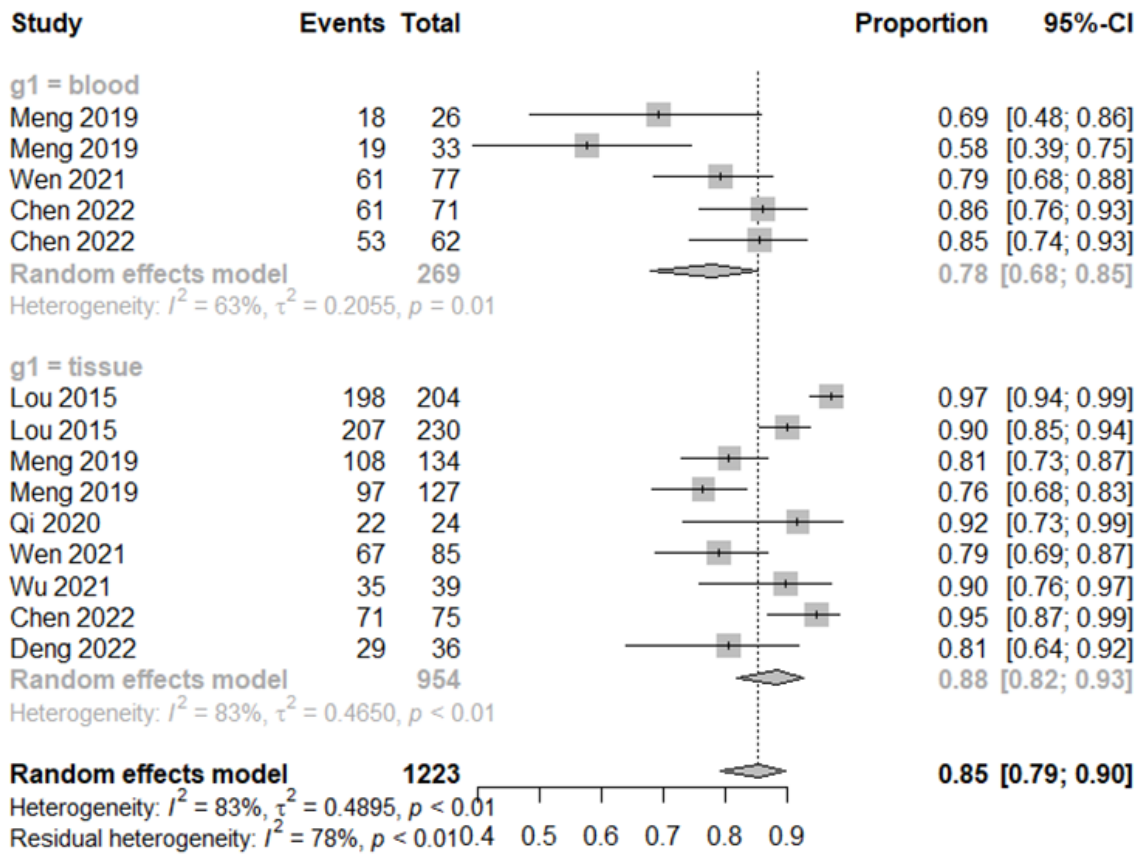


Figure 4. Forest plots of diagnostic odds ratios (A), sensitivities (B), and specificities (C) of the serum and tissue eosinophil levels.

shown in Supplementary Tables 2 and 3. The individual grading of all studies was conducted by two researchers, and a composite score was derived by averaging the assessments provided by both reviewers. The evidence pertaining to the quality of the encompassed studies fell within the range of 6 to 7. Based on the interpretation of the Newcastle Ottawa scale, scores within the 6-7 range are regarded as indicative of high quality. Consequently, the inclusion of these studies in the analysis is deemed to be of good/ high quality.

The laboratory, clinical, and pathological features of patients with recurrent CRSwNP and others

In terms of the laboratory findings, the percentage and count of blood eosinophils (SMD = 0.3432 [0.0668; 0.6195], I^2 = 95.5%) and those of tissue eosinophils (SMD = 3.1995 [2.3801; 4.0190], I^2 = 98.7%) were higher in RNP than non-RNP subjects (Figure 2A–C). In terms of clinical features, all of nasal obstruction (SMD = 0.6610 [0.1252; 1.1968], I^2 = 95.0%), the total nasal symptom score (SMD = 0.4243 [0.1585; 0.6901], I^2 = 85.2%), subjective olfactory dysfunction (SMD = 1.5962 [0.4775; 2.7149], I^2 = 98.3%), and the rate of endoscopically detected polyps (SMD = 0.3114 [0.0243; 0.5984], I^2 =89.5%) were higher in RNP than non-RNP subjects (Figure 3A–C). In terms of radiological findings, the Lund-Mackey CT score (SMD = 0.7420 [0.4412; 1.0428] I^2 = 91.1%) was higher in RNP than non-RNP subjects (Figure 4). In contrast, the count and percentage of tissue neutrophils (SMD = –1.1463 [–2.0088; –0.2837], I^2 = 95.9%) were lower in RNP than in non-RNP subjects. However, there were no significant between-group differences in facial pain/headache (SMD = 0.7389 [–0.1390; 1.6168], I^2 = 97.9%), rhinorrhea (SMD = 0.0197 [–0.2478; 0.2872], I^2 = 80.1%), or the count or percentage of blood neutrophils (SMD = 0.6420 [–0.3327; 1.6167], I^2 = 98.4%). Begg funnel plots and Egger tests of the Lund-Mackey CT score (p = 0.751), subjective olfactory dysfunction (p = 0.8749), endoscopic polyp score (p = 0.5107), facial pain (p = 0.8288), nasal obstruction (p = 0.567), rhinorrhea (p = 0.6094), total nasal symptom score (p = 0.2886), and the count and percentage of blood eosinophils (p = 0.089) suggested no publication bias. The count and percentage of tissue eosinophils (p < 0.001) were potentially biased. However, the trim and fill test revealed no significant difference between the observed and adjusted values (3.1995, p < 0.0001 vs. 2.3266, p < 0.0001]. Therefore, we conclude that there was no publication bias. The Begg funnel plot results are shown in Supplementary Figure 1. Publication

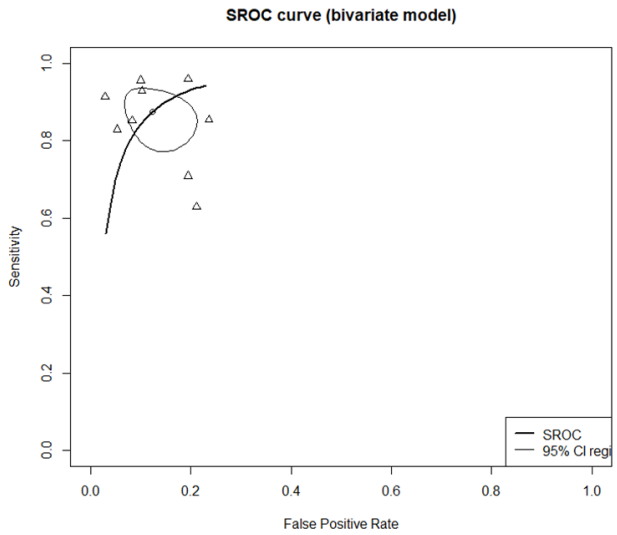


Figure 5. The area under the summary receiver operating characteristic of the tissue eosinophil level.

bias in terms of the neutrophil count and percentage could not be assessed given the small number of studies (< 10).

Comparison of comorbidities in recurrent CRSwNP and non-recurrent CRSwNP patients

Aspirin-intolerance (OR = 3.0968 [2.3225; 4.1291], I^2 = 6.1%), allergic rhinitis (OR = 1.7844 [1.4304; 2.2260], I^2= 30.4%), atopy (OR = 1.3925 [1.0366; 1.8706], I^2 = 55.2%), and asthma (OR = 2.5620 [2.3172; 2.8326], I2 = 42.3%) were associated with RNP. Also, eosinophilic chronic sinusitis (OR = 2.8069 [1.5387; 5.1202], I^2 = 71.3%) was associated with RNP.

Begg funnel plots and Egger tests of allergic rhinitis (p = 0.08494), aspirin-intolerance (p = 0.09311), and atopy (p = 0.5801) showed no publication bias. The Egger test (p = 0.004675) and the Begg funnel plot for asthma suggested publication bias. However, the Duval and Tweedie trim and fill test revealed no significant difference (2.5620, p < 0.0001 vs. 2.2622, p < 0.0001). Therefore, the risk of publication bias was low.

Diagnostic accuracy of serum and tissue eosinophil levels in terms of recurrent CRSwNP

Seven studies assessed the diagnostic accuracies of the eosinophil levels. The DOR for the count and percentage of tissue eosinophils in RNP patients was 54.1247 ([20.1194; 145.6050], I^2 = 87.6%). The AUC was 0.936 (Figure 5). The sensitivity and specificity were 0.8809 ([0.8078; 0.9287], I^2 = 81.2%) and 0.8834 ([0.8192; 0.9268], I^2 = 82.6%) , respectively. However, the DOR for the count or percentage of serum eosinophils in RNP patients was 3.8632 [2.0669; 7.2208], I^2 = 63.1%). The AUC was 0.549. The sensitivity and specificity were 0.5367 ([0.4941; 0.5788], I^2 = 0.0%) and 0.7779 ([0.6792; 0.8528], I^2 = 76.7%) , respectively. The RNP serum eosinophil level thus evidenced a lower diagnostic power than the tissue eosinophil level (sensitivity: 0.8809 vs. 0.5367, p < 0.0001; specificity: 0.8834 vs. 0.7779, p = 0.0354; DOR: 54.1247 vs. 3.8632, p < 0.0001).

Sensitivity analyses and meta regression

We eliminated each study individually and repeated the meta-analysis. All results agreed with those described above. The utilization of meta-regression analysis to assess the impact of follow-up periods yielded no significant effect on the estimates of SMD, OR, sensitivity, specificity, and diagnostic accuracy pertaining to laboratory, clinical, and pathological features, as well as underlying comorbidities, except for the percentage and count of tissue neutrophils (p = 0.04). It is noteworthy, however, that the SMD analysis of tissue neutrophils was based on only four studies, which might not provide adequate insight into the influence of follow-up periods. Therefore, additional studies are warranted to further elucidate this matter.

Discussion

When treating CRSwNP patients, most guidelines recommend initial prescription of a corticosteroid nasal spray and nasal irrigation. After follow-up, medical treatment is given if the symptoms do not improve, followed by ESS if there is still no improvement[1, 2]. However, CRSwNP is associated with a high RNP rate even after ESS[47]; long follow-up is essential. Mucosal conditions can be managed via intensive follow-up or specific drug treatment. It is important that clinicians be aware of RNP factors in patients undergoing ESS surgery. However, to the best of our knowledge, no meta-analysis of factors predicting RNP has yet appeared. Currently, The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020 guideline suggests blood and tissue eosinophil levels as markers that can help predict RNP[1]. However, the extensive investigation of the relative prognostic significance of these factors has been lacking. Also, the International Consensus statement on Allergy and Rhinology (ICAR) 2021 did not mention this topic[2].

We identified various risk factors associated with RNP. Extensive CRSwNP with a high nasal symptom score or a high Lund Mackey CT score was associated with postoperative RNP. Of the nasal symptoms, nasal obstruction and olfactory dysfunction were closely related, but the facial pain/headache symptom score and the rhinorrhea symptom score less so. In patients with eosinophilic CRS, olfactory dysfunction is more severe than in others, and associated with poorer outcomes[14]. All elevated serum and tissue eosinophil/neutrophil numbers; more comorbidities; allergic conditions including allergic rhinitis, atopy and asthma; and aspirin-intolerance were related to RNP. Thus, in general, type 2 inflammation is strongly linked to RNP. The fact that tissue eosinophilia better predicts RNP than does serum eosinophilia emphasizes the need to collect tissues during ESS surgery and

then analyze them. Also, although the serum neutrophil levels did not differ between the RNP and non-RNP groups, the fact that the tissue neutrophil level was lower in the RNP group also indicates the importance of tissue eosinophil/neutrophil analyses. In particular, tissue eosinophilia usefully identifies type 2 inflammation[1]. We confirmed that tissue eosinophilia alone well-predicted RNP.

Eosinophilic CRS is gaining increasing attention in Asia. Early studies found that Asian patients evidenced more neutrophil-dominant (Th1/Th17) disease than Western patients[48], but recent studies have confirmed that the proportion of type 2 signatures is much higher in Asian patients[49].

Treatments for eosinophilic CRSwNP are under development. Although eosinophilic CRSwNP responds well to corticosteroids, long-term administration of such drugs causes various side-effects including disruption of the hormonal system. Recently, monoclonal antibodies that reduce type 2 inflammation, including anti-immunoglobin E, anti-interleukin-4/13, and anti-interleukin-5 or -5 receptor-α antibodies have become commercially available[50]. Although issues in terms of cost-effectiveness and the persistence of effects after drug discontinuation remain, these are promising alternatives to systemic corticosteroids.

In terms of surgery, it has been reported that "reboot" surgery effectively removes type 2-inflamed mucosa[51]; this has been confirmed[52]. Given the intractability of eosinophilic CRSwNP and the increasing number of patients, research on various treatment methods must continue.

This meta-analysis had several limitations. First, access to healthcare by country, institutional setting, post-operative care, differences in CRSwNP characteristics according to race, underlying diseases, definition of CRSwNP severity, primary ESS extent, patient compliance and differences in endoscopic polyp scoring according to raters may have affected the results. Due to the nature of the included studies, the impact of primary ESS methods or postoperative care by institution is considered to be an unavoidable cause of heterogeneity due to the nature of meta-analysis Large clinical trials with similar patient populations and standardized protocols are needed. Second, the data were collected from only a few regions (26/33 studies were from East and South Asia); geographical and genetic factors may influence clinical characteristics. Third, in most studies, follow-up was no longer than 2 years. Long-term, well-designed, large-scale studies are needed.

Conclusion

Through this meta-analysis, various risk factors of postoperative RNP were identified, and it was confirmed that tissue eosinophil level alone could be used as a useful predictor of postoperative RNP.

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The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see:
http://www.textcheck.com/certificate/kCc1OI

Authorship contribution

DHK, SHH, contributed to study design, data collection, interpretation of results, drafting and critical evaluation of the final manuscript. JSH, GK, MAB contributed to study design, interpretation of results, drafting and critical evaluation of the final manuscript. SWK contributed to interpretation of results and critical evaluation of the final manuscript.

Conflict of interest

None declared.

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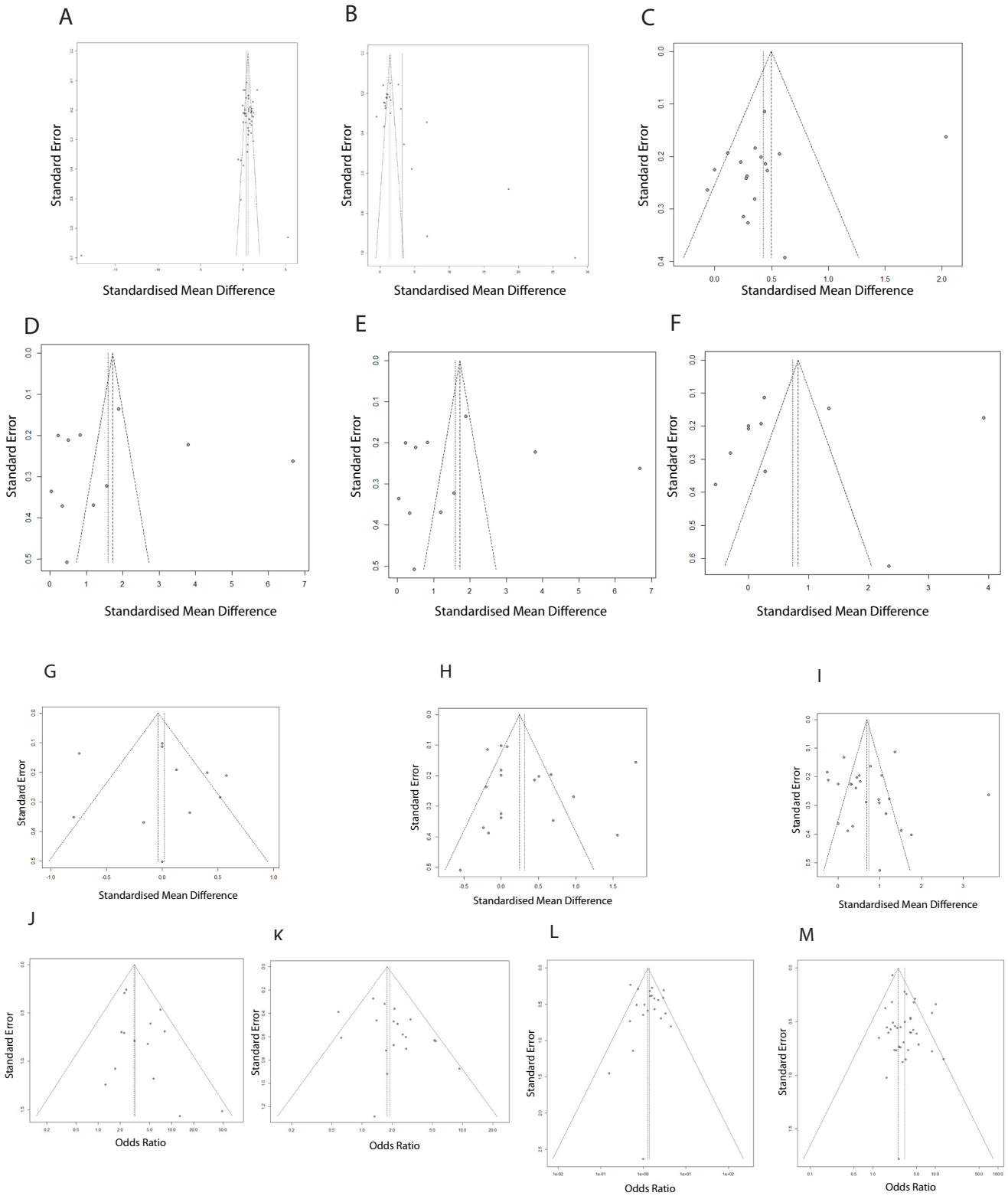
This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL



Supplementary Figure 1. Begg funnel plots. (A) blood eosinophil level, (B) tissue eosinophil level, (C) total nasal symptom score, (D) nasal obstruction symptom score, (E) subjective olfactory dysfunction, (F) facial pain/headache symptom score, (G) rhinorrhea symptom score, (H) endoscopic nasal polyp score, (I) Lund Mackey CT score, (J) aspirin-intolerance, (K) allergic rhinitis, (L) atopy, and (M) asthma.

Supplementary Table 1. Search terms and queries.

Database	Search	Search terms and queries
PubMed	#1	"Nasal Polyps"[Mesh]
	#2	"Nasal Polyps"[TW] OR "Nasal Polyp"[TW] OR "Polyp, Nasal"[TW] OR "Polyps, Nasal"[TW] OR "Chronic rhinosinusitis with nasal polyps"[TW] OR "CRSwNP"[TW]
	#3 Combine	#1 OR #2
	#4	"Rhinosinusitis"[TW] OR "Chronic rhinosinusitis"[TW] OR "recurrent chronic rhinosinusitis"[TW] OR "Chronic rhinosinusitis with nasal polyps"[TW] OR "CRSwNP"[TW]
	#5	"Rhinitis"[Mesh]
	#6	"Rhinitis"[TW] OR "Rhinitides"[TW] OR "Nasal Catarrh"[TW] OR "Catarrh, Nasal"[TW] OR "Catarrhs, Nasal"[TW] OR "Nasal Catarrhs"[TW]
	#7	"Sinusitis"[Mesh]
	#8	"Sinusitis"[TW] OR "Sinusitides"[TW] OR "Sinus Infections"[TW] OR "Infection, Sinus"[TW] OR "Infections, Sinus"[TW] OR "Sinus Infection"[TW]
	#9 Combine	#4 OR #5 OR #6 OR #7 OR #8
	#10	"Chronic Disease"[Mesh]
	#11	"Chronic Disease"[TW] OR "Chronic Diseases"[TW] OR "Disease, Chronic"[TW] OR "Chronic Illness"[TW] OR "Chronic Illnesses"[TW] OR "Illness, Chronic"[TW] OR "Chronic Condition"[TW] OR "Chronic Conditions"[TW] OR "Condition, Chronic"[TW] OR "Chronically Ill"[TW] OR "Chronic rhinosinusitis"[TW] OR "Chronic rhinosinusitis with nasal polyps"[TW] OR "CRSwNP"[TW]
	#12 Combine	#10 OR #11
	#13 Combine	#3 AND #9 AND #12
	#14	"Recurrence"[Mesh]
	#15	"Recurrence"[TW] OR "Recurrences"[TW] OR "Recrudescence"[TW] OR "Recrudescences"[TW] OR "Relapse"[TW] OR "Relapses"[TW] OR "recurrent"[TW] OR "postoperative"[TW] OR "CRSwNP Recurrence"[TW]
	#16 Combine	#14 OR #15
	#17 Combine	#13 AND #16
	#18 Limit	#17 NOT ("animals"[MeSH] NOT "Humans"[MeSH])
Database	**Search**	**Search terms and queries**
EMBASE	#1	"nose polyp"/exp
	#2	"Nasal Polyps":ti,ab,kw,de OR "Nasal Polyp":ti,ab,kw,de OR "Polyp, Nasal":ti,ab,kw,de OR "Polyps, Nasal":ti,ab,kw,de OR "Chronic rhinosinusitis with nasal polyps":ti,ab,kw,de OR "CRSwNP":ti,ab,kw,de
	#3 Combine	#1 OR #2
	#4	"Rhinosinusitis":ti,ab,kw,de OR "Chronic rhinosinusitis":ti,ab,kw,de OR "recurrent chronic rhinosinusitis":ti,ab,kw,de OR "Chronic rhinosinusitis with nasal polyps":ti,ab,kw,de OR "CRSwNP":ti,ab,kw,de
	#5	"rhinitis"/exp
	#6	"Rhinitis":ti,ab,kw,de OR "Rhinitides":ti,ab,kw,de OR "Nasal Catarrh":ti,ab,kw,de OR "Catarrh, Nasal":ti,ab,kw,de OR "Catarrhs, Nasal":ti,ab,kw,de OR "Nasal Catarrhs":ti,ab,kw,de
	#7	"sinusitis"/exp
	#8	"Sinusitis":ti,ab,kw,de OR "Sinusitides":ti,ab,kw,de OR "Sinus Infections":ti,ab,kw,de OR "Infection, Sinus":ti,ab,kw,de OR "Infections, Sinus":ti,ab,kw,de OR "Sinus Infection":ti,ab,kw,de
	#9 Combine	#4 OR #5 OR #6 OR #7 OR #8
	#10	"chronic disease"/exp
	#11	"Chronic Disease":ti,ab,kw,de OR "Chronic Diseases":ti,ab,kw,de OR "Disease, Chronic":ti,ab,kw,de OR "Chronic Illness":ti,ab,kw,de OR "Chronic Illnesses":ti,ab,kw,de OR "Illness, Chronic":ti,ab,kw,de OR "Chronic Condition":ti,ab,kw,de OR "Chronic Conditions":ti,ab,kw,de OR "Condition, Chronic":ti,ab,kw,de OR "Chronically Ill":ti,ab,kw,de OR "Chronic rhinosinusitis":ti,ab,kw,de OR "Chronic rhinosinusitis with nasal polyps":ti,ab,kw,de OR "CRSwNP":ti,ab,kw,de
	#12 Combine	#10 OR #11
	#13 Combine	#3 AND #9 AND #12
	#14	"recurrent disease"/exp

Database	Search	Search terms and queries
	#15	"Recurrence":ti,ab,kw,de OR "Recurrences":ti,ab,kw,de OR "Recrudescence":ti,ab,kw,de OR "Recrudescences":ti,ab,kw,de OR "Relapse":ti,ab,kw,de OR "Relapses":ti,ab,kw,de OR "recurrent":ti,ab,kw,de OR "postoperative":ti,ab,kw,de OR "CRSwNP Recurrence":ti,ab,kw,de
	#16 Combine	#14 OR #15
	#17 Combine	#13 AND #16
	#18 Limit	#17 NOT ('animal'/exp NOT 'human'/exp)
Database	**Search**	**Search terms and queries**
Cochrane Library	#1	[mh "Nasal Polyps"]
	#2	"Nasal Polyps":ti,ab,kw OR "Nasal Polyp":ti,ab,kw OR "Polyp, Nasal":ti,ab,kw OR "Polyps, Nasal":ti,ab,kw OR "Chronic rhinosinusitis with nasal polyps":ti,ab,kw OR "CRSwNP":ti,ab,kw
	#3 Combine	#1 OR #2
	#4	"Rhinosinusitis":ti,ab,kw OR "Chronic rhinosinusitis":ti,ab,kw OR "recurrent chronic rhinosinusitis":ti,ab,kw OR "Chronic rhinosinusitis with nasal polyps":ti,ab,kw OR "CRSwNP":ti,ab,kw
	#5	[mh "Rhinitis"]
	#6	"Rhinitis":ti,ab,kw OR "Rhinitides":ti,ab,kw OR "Nasal Catarrh":ti,ab,kw OR "Catarrh, Nasal":ti,ab,kw OR "Catarrhs, Nasal":ti,ab,kw OR "Nasal Catarrhs":ti,ab,kw
	#7	[mh "Sinusitis"]
	#8	"Sinusitis":ti,ab,kw OR "Sinusitides":ti,ab,kw OR "Sinus Infections":ti,ab,kw OR "Infection, Sinus":ti,ab,kw OR "Infections, Sinus":ti,ab,kw OR "Sinus Infection":ti,ab,kw
	#9 Combine	{OR #4-#8}
	#10	[mh "Chronic Disease"]
	#11	"Chronic Disease":ti,ab,kw OR "Chronic Diseases":ti,ab,kw OR "Disease, Chronic":ti,ab,kw OR "Chronic Illness":ti,ab,kw OR "Chronic Illnesses":ti,ab,kw OR "Illness, Chronic":ti,ab,kw OR "Chronic Condition":ti,ab,kw OR "Chronic Conditions":ti,ab,kw OR "Condition, Chronic":ti,ab,kw OR "Chronically Ill":ti,ab,kw OR "Chronic rhinosinusitis":ti,ab,kw OR "Chronic rhinosinusitis with nasal polyps":ti,ab,kw OR "CRSwNP":ti,ab,kw
	#12 Combine	#10 OR #11
	#13 Combine	#3 AND #9 AND #12
	#14	[mh "Recurrence"]
	#15	"Recurrence":ti,ab,kw OR "Recurrences":ti,ab,kw OR "Recrudescence":ti,ab,kw OR "Recrudescences":ti,ab,kw OR "Relapse":ti,ab,kw OR "Relapses":ti,ab,kw OR "recurrent":ti,ab,kw OR "postoperative":ti,ab,kw OR "CRSwNP Recurrence":ti,ab,kw
	#16 Combine	#14 OR #15
	#17 Combine	#13 AND #16
Database	**Search**	**Search terms and queries**
Web of Science	#1	TS=("Nasal Polyp" OR "Chronic rhinosinusitis with nasal polyps" OR "CRSwNP")
	#2	TS=("Rhinosinusitis" OR "Rhinitis" OR "Sinusitis")
	#3	TS=("Chronic Disease" OR "Chronic rhinosinusitis" OR "CRSwNP" OR "Chronic")
	#4	TS=("Recurrence" OR "recurrent" OR "Relapse" OR "postoperative")
	#5 Combine	(#1 AND #2 AND #3) AND #4
Database	**Search**	**Search terms and queries**
Google Scholar	#1	"Nasal Polyp" OR "Chronic rhinosinusitis with nasal polyps" OR "CRSwNP"
	#2	"Rhinosinusitis" OR "Rhinitis" OR "Sinusitis"
	#3	"Chronic"OR "Chronic rhinosinusitis" OR "CRSwNP"
	#4	"Recurrence" OR "recurrent" OR "Relapse" OR "postoperative"
	#5 Combine	("Nasal Polyp" OR "Chronic rhinosinusitis with nasal polyps" OR "CRSwNP") AND ("Rhinosinusitis" OR "Rhinitis" OR "Sinusitis") AND ("Chronic"OR "Chronic rhinosinusitis" OR "CRSwNP") AND ("Recurrence" OR "recurrent" OR "Relapse" OR "postoperative")

Supplementary Table 2. Study characteristics.

Study	Study design	Number of patients	Age	Sex (M/F)	Nation	Outcomes	Follow-up (month)
Matsuwaki 2008	Cohort	56	43.1 (18-80)	39/17	Japan	percentage and count of serum and tissue eosinophil/ incidence of asthma, allergy/ percentage of tissue eosinophil/ endoscopic polyp score/ CT	60
Akhtar 2010	Cohort	192	33 .9±12.9	120/72	Pakistan	incidence of allergy, asthma/ rhinorrhea, facial pain, olfactory dysfunction / CT	38 (24-60)
Van Zele 2014	Cohort	36	50.23 (4.33)	19/17	USA	Incidence of allergy, asthma, aspirin intolerance/ endoscopic polyp score/ CT/ nasal obstruction, rhinorrhea, olfactory dysfunction, facial pain	75.96
Brescia 2015	Cohort	179	51.8±15.3	117/62	Italy	incidence of allergy, asthma, aspirin intolerance, and eosinophilic sinusitis/ count and percentage of serum eosinophil	32.8±14.7
Lou 2015	Cohort	387	46.1±13.2	214/173	China	Incidence of allergy, asthma/ percentage of tissue eosinophil/ endoscopic polyp score/ CT/ olfactory dysfunction, rhinorrhea, nasal obstruction, facial pain/ percentage and count of tissue and serum eosinophil and neutrophil/ diagnostic power of tissue eosinophil percentage and count	34.03 (4.95)
Yenigun 2015	Cross-sectional	158	29.40±5.44	102/56	Turkey	Count of serum eosinophil and neurtolphil	Non specified
Li 2016	Cohort	210	46 (28-56)	136/74	China	Incidence of allergy/ total nasal symptom score/ CT	24
Nakayama 2016	Cross-sectional	36	54.5±13.8	27/9	Japan	Incidence of eosinophilic sinusitis, allergic rhinitis, asthma, aspirin intolerance/ endoscopic polyp score/ CT/ nasal obstruction, rhinorrhea, facial pain, olfactory dysfunction/ count of serum eosinophil	36.9±10.3
Brescia 2017	Cohort	280	49.5±15.1	174/106	Italy	incidence of allergy, ashma, aspirin intolerance/ eosinophilc count and percentage and percentage of eosinophil	32.7±12.1
Lee 2017	Cohort	36	49 (18-60)	25/11	China	Count of tissue and serum eosinophil/ nasal obstruction, rhinorrhea, olfactory dysfunction, facial pain/ endoscopic polyp score	>12
Calus 2019	Cohort	38	44 (31-54)	25/13	Belgium	incidence of allergy, asthma, aspirin intolerance and score of nasal polyp and total symptom score, and level of Total IgE	720
Meng 2019	Cohort	230	44.7±3.4	128/102	China	Incidence of allergy, asthma/ score of total nasal symptom, nasal obstruction, rhinorrhea, olfactory dysfunction, facial pain, CT, nasal polyp/percentage and count of serum and tissue eosinophil/diagnostic power of percentage and coung of tissue and serum eosinophil	32.7±12.1
Du 2020	Cohort	96	48.7 (14.0)	76/20	China	incidence of allergy, asthma, aspirin intolerance, and serum of eosinophil/ CT/ percentage of serum eosinophil	45
Mortuaire 2020	Cohort	48	49.5±13.8	30/18	France	Incidence of allergy, asthma, aspirin intolerance/ endoscopic polyp score/ CT /total nasal symptom/ count of serum eosinophil	80.4(16.8)
Nakamaru 2020	Cohort	69	55.3±13.3	34/35	Japan	Incidence of allergy, asthma, aspirin intolerance, count of tissue eosinophil/ CT/ endoscopic polyp score/count of tissue and serum eosinophil	Non specified
Qi 2020	Cohort	51	43.7 (11.0)	30/21	China	Incidence of asthma, allergic rhinitis/ nasal obstruction, rhinorrhea, facial pain, olfactory dysfunction/ CT/ endoscopic polyp score/ percentage of tissue and serum eosinophil and neutrophil/diagnostic power of tissue eosinophil percentage	12-18
Salvador 2020	Cohort	132	43.4±11.5	82/50	Portugal	Incidence of allergic rhinitis, allergy, asthma, aspirin intolerance/endoscopic polyp score/ CT/ count of serum eosinophil	38.4±18
Wu 2020	Cohort	107	42.0±17.17	60/20	Taiwan	Incidcence of asthma, allergy/percentage of serum eosinophil/ total nasal symptom/ endoscopic polyp score/ CT	>60

Study	Study design	Number of patients	Age	Sex (M/F)	Nation	Outcomes	Follow-up (month)
Gan 2021	Cohort	77	48.62±6.33	34/43	China	incidence of allergy, asthma/ total nasal symptom/ CT/ count of tissue and serum of eosinophil and neutrophil	12
Lu 2021	Cohort	58	48 (36-57)	43/15	Taiwan	Incidence of allergy, asthma/ count of serum and tissue eosinophil/ CT	27.9 ± 15.5
Peng 2021	Cohort	432	47.0±12.3	201/190	China	Incidence of allergy, aspirin intolerance, asthma/endoscopic polyp score/ count of serum eosinophil	>24
Wang 2021	Cohort	203	46.6±4.1	181/132	China	Incidece of allergy, asthma/endoscopic polyp score/ nasal obstruction, rhinorrhea, olfactory dysfunction, facial pain, total nasal symptom/ percentage of serum eosinophil and count of tissue eosinophil	24
Wen 2021	Cohort	120	43.3±12.5	71/49	China	Incidence of allergic rhinitis, asthma, eosinophilic sinusitis/ total nasal symptom/ CT/count and percentage of tissue and serum eosinophil/ diagnostic power of tissue and serum eosinophil count and percentage	Non specified
Wu 2021	Cohort	108	44.8±12.1	69/39	China	Incidence of asthma, allergy/ nasal obstruction, rhinorrhea, facial pain, olfactory dysfunction/ endoscopic polyp score/ CT/ percentage of serum eosinophil and neutrophil / diagnostic power of tissue eosinophil percentage	Non specified
Chen 2022	Cohort	133	42.0 (29.0-52.0)	89/44	China	incidence of allergy, asthma, allergic rhinitis, aspirin intolerance/ nasal obstruction, rhinorrhea, facial pain, olfactory dysfuction, total nasal symptom/ endoscopic polyp score/ CT/count and percentage of neutrophil and eosinophil	12
Chen 2022	Cohort	110	44.0 (32.0-51.500	72/38	China	incidence of allergy, asthma, allergic rhinitis, ASA intolerance, and eosinophilc sinusitis and score of nasal obstruction, rhinorrhea, facial pain, olfactory dysfunction, and count and percentage of serum and tissue eosinophil	24
Deng 2022	Cohort	60	40.1±11.4	38/22	China	incidence of allergy, asthma/ count and percentage of tissue and serum eosinophil/ total nasal symptom/ CT/ diagnostic value of tissue eosinophil percentage	Non specified
Wang 2022	Cohort	72	41.0±10.9	33/39	China	Incidcence of asthma, allergy/count and percentage of serum eosinophil/ total nasal symptom/ endoscopic polyp score/ CT	Non specified
Wang 2022	Cohort	99	43.1±17.2	58/41	China	Incidence of allergy, allergic rhinitis, asthma, eosinophilic sinusitis/ count and percentage of serum and tissue eosinophil/ total nasal symptom/ endoscopic polyp score/ CT	Non specified
Yu 2022	Cohort	210	52.8±13.7	167/43	Korea	Incidence of eosinophil sinusitis, asthma, allergic rhinitis/ CT/ count of tissue eosinophil and percentage of serum eosinophil and neutrophil	12
Zhang 2022	Cohort	110	41.4±10.7	59/51	China	Incidence of allergic rhinitis, asthma, eosinophilic sinusitis/ count and percentage of tissue eosinophil/ total nasal symptome/ CT/count and percentage of tissue amd serum eosinophil	24
Zhang 2022	Cohort	124	33.1±8.8	74/50	China	Incidence of allergy, allergic rhirnitis, asthma/ count and percentage of tissue and serum eosinophil/ CT/ endoscopic polyp score/ total nasal symptom	36
Zhang 2022	Cohort	80	40.7±10.4	37/33	China	Incidence of allergic rhinitis, asthma/ count and percentage of serum eosinophil/ score of total nasal symptom/ CT/ count and percentage of serum eosinophil	Non specified

Supplementary Table 3. Quality (risk of bias) assessment.

Study (year)	Selection [a]				Comparability [b]		Exposure [c]			The Newcastle-Ottawa Scale
	1	2	3	4	5A	5B	6	7	8	
Matsuwaki 2008	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	6
Akhtar 2010	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	7
Van Zele 2014	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	7
Brescia 2015	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	6
Lou 2015	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	7
Yenigun 2015	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
Li 2016	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	7
Nakayama 2016	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
Brescia 2017	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
Lee 2017	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	6
Calus 2019	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
Meng 2019	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	7
Du 2020	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	6
Mortuaire 2020	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
Nakamaru 2020	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	7
Qi 2020	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	6
Salvador 2020	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
Wu 2020	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	6
Gan 2021	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	7
Lu 2021	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	6
Peng 2021	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	7
Wang 2021	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
Wen 2021	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	7
Wu 2021	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
Chen 2022	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
Chen 2022	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	6
Deng 2022	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	7
Wang 2022	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	6
Wang 2022	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	7
Yu 2022	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
Zhang 2022	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	7
Zhang 2022	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
Zhang 2022	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7

A star rating system was used to indicate the quality of a study, with a maximum of nine stars. A study could be awarded a maximum of one star for each numbered item within the selection and exposure categories.

[a] Selection (4 items): adequacy of case definition; representativeness of the cases; selection of controls; and definition of controls.

[b] Comparability (1 item): comparability of cases and controls based on the design or analysis.

[c] Exposure (3 items): ascertainment of exposure; same method of ascertainment for cases and controls; and non-response rate (same rate for both groups).