

Original Article



Clinical and Laboratory Features of Various Criteria of Eosinophilic Chronic Rhinosinusitis: A Systematic Review and Meta-Analysis

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- **Objectives.** The aim of this study was to evaluate the differences in clinical and laboratory features between eosinophilic chronic rhinosinusitis (ECRS) and non-ECRS and to compare diagnostic criteria for ECRS.
- **Methods.** We compared clinical features and/or laboratory findings classified as ECRS and non-ECRS according to various diagnostic criteria (histological and clinical). We also analyzed studies to compare endoscopic findings, symptom scores, laboratory findings, and computed tomography (CT) findings between ECRS and non-ECRS.
- **Results.** Our search included 55 studies with 6,143 patients. A comparison of clinical features and/or laboratory criteria with histological criteria showed no significant differences in nasal symptom scores and CT scores according to criteria. Serum eosinophil levels showed differences across the criteria, with ECRS consistently characterized by higher serum eosinophil levels than non-ECRS. Among the four criteria, the Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis (JESREC) criteria and tissue eosinophili (≥70) were associated with decreased olfactory function. In laboratory findings, the eosinophil percentage (standardized mean difference [SMD], 1.561; 95% confidence interval [CI], 1.329–1.794; *P*<0.001) and eosinophil count (SMD, 1.493; 95% CI, 1.134–1.852; *P*<0.001) of eosinophils were higher in ECRS than non-ECRS. In clinical findings, nasal symptom scores (SMD, 0.382; 95% CI, 0.156–0.608; *P*<0.001), endoscopic nasal polyp scores (SMD, 0.581; 95% CI, 0.314–0.848; *P*<0.001), and olfactory dysfunction (SMD, 0.416; 95% CI, 0.037–0.794; *P*=0.031) were higher in ECRS than in non-ECRS. With regard to CT findings, the whole-sinus opacification score (SMD, 0.824; 95% CI, 0.588–1.059; *P*<0.001) was higher in ECRS than in non-ECRS. In particular, there were significant differences in anterior ethmoid sinus and sphenoid sinus opacification.
- **Conclusion.** ECRS and non-ECRS differ in their clinical and laboratory features. When histological confirmation is difficult on an outpatient basis, ECRS could be diagnosed using clinical features and/or laboratory findings.

Keywords. Eosinophils; Sinusitis; Biomarker; Endoscopy; Tomography; X-Ray Computed

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Chronic rhinosinusitis (CRS) is a common chronic otolaryngological disease, the classification and treatment of which are still being discussed. Patients with CRS have generally been classified according to their clinical phenotype (i.e., with or without polyps). In recent years, CRS patients have been classified according to endotype, which characterizes the pathogenesis of the disease according to the inflammatory process [1]. Based on

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the presence or absence of tissue eosinophilic infiltration, CRS can also be divided into eosinophilic CRS (ECRS) and non-ECRS subtypes [2]. Eosinophilic and non-eosinophilic airway inflammation can present with several different clinical symptoms [3]. Non-ECRS can be controlled relatively well with a combination of endoscopic sinus surgery and low-dose macrolide therapy. By contrast, in patients with ERCS, nasal polyps tend to recur frequently after endoscopic sinus surgery [4]. In addition, ECRS does not respond well to macrolide therapy, but shows a good initial response to systemic steroid therapy in recurrent cases [4].

A number of studies have compared the differences between ECRS and non-ECRS with nasal polyps, but no consensus yet exists regarding the histopathological criteria for diagnosis [4]. Some studies have defined ECRS using various tissue eosinophilia cutoff values, such as 5, 8, 10, 70, 100, or 120 eosinophils per high-power field (HPF; \times 400), whereas others have defined it using the proportion of eosinophils to the total number of inflammatory cells based on various cutoff values such as 5%, 10%, 11%, 20%, or up to 50%. Inconsistencies also exist regarding the measurement method. The Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis (JESREC) proposed criteria for defining ECRS that were based not on tissue eosinophilia, but on a scoring system composed of clinical findings, such as disease site (bilateral sinus involvement), the presence of nasal polyps, computed tomography (CT) findings (soft tissue density in ethmoid sinuses compared to the maxillary sinuses), and serum eosinophilia [5]. As the treatment strategy differs for ECRS and non-ECRS, it would be useful to have an effective standard for diagnosing ECRS in outpatient clinics without the need to collect and analyze sinus tissue or nasal polyps [4]. Therefore, we analyzed the clinical and laboratory features of ECRS and non-ECRS and compared the criteria that can be used in the clinic without nasal biopsy with histopathological criteria.

HIGHLIGHTS

- The histological and clinical criteria showed similar trends in nasal symptoms, computed tomography (CT), and serum eosinophil levels.
- Higher endoscopic polyp and nasal symptom scores and elevated serum eosinophil counts are associated with eosinophilic chronic rhinosinusitis (ECRS).
- Opacification of the anterior ethmoid or sphenoid sinuses on CT is associated with ECRS.
- When it is difficult to diagnose ECRS on an outpatient basis, clinical and laboratory features can be used.

MATERIALS AND METHODS

Study protocol and registration

This systematic review and meta-analysis is described with reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [6]. This study protocol was registered prospectively on Open Science Framework (https://osf.io/ enb3j).

Literature search

Clinical studies were identified in PubMed, Scopus, Embase, the Web of Science, and the Cochrane Central Register of Controlled Trials up to November 2021. The search terms were as follows: "sinusitis," "nasal polyps," "eosinophils," "cell count," "eosinophilic chronic sinusitis," "blood eosinophil percentage," "olfactory," "nasal endoscopy score," "computed tomography score," "symptom," and "visual analog scale." Two reviewers (DHK and MAB) independently reviewed the titles and abstracts of candidate studies in each database and excluded irrelevant studies. If the two reviewers did not agree on a paper, its eligibility for inclusion was determined through discussion with a third reviewer (SWK). Papers that lacked quantifiable or relevant data were excluded after a full-text review. References of included studies were also searched to ensure that no related studies were omitted.

Selection criteria

Inclusion criteria were as follows: patients underwent clinical or imaging studies on ECRS, prospective or retrospective study, comparison of clinical or imaging data with non-ECRS data, and data on results of mean differences or odds ratio (OR) analyses. Exclusion criteria were as follows: case report; review article; report of other rhinological disease, such as rhinitis or septal deviation; non-English language article; and lack of laboratory, clinical, or imaging data for statistical analysis. The search and selection strategy is summarized in Fig. 1.

Data organization and risk of bias assessment

Data were extracted from selected eligible studies and organized in a standardized format [7,8]. We abstracted data on numbers of patients, sex, nationality, diagnostic criteria, outcomes of additional tests performed to evaluate ECRS, and the *P*-values for comparisons of ECRS and non-ECRS. Analyzed outcomes were the percentage or absolute count of eosinophils [3-5,9-51], total non-specific immunoglobulin E (IgE) [3,4,13,15,16,19,21-23,30,35,39-41,48,52-54], endoscopic polyp score [3,9,28-30,32,33,37,38,40,41,43,51,52,54-59], nasal symptomatic score [3,31,33,37,40,41,46,50-52,55-58,60], olfactory function [23,25-27,30,37,41,42,48,56], CT score [3,4,9-14,16,23-26,28-33,35,37,38,40,41,43-45,47,48,50-53,55-61], and the odd ratios of comorbidities associated with ECRS (allergic rhinitis, asthma, occurrence of nasal polyp, bi-laterality of nasal polyp)

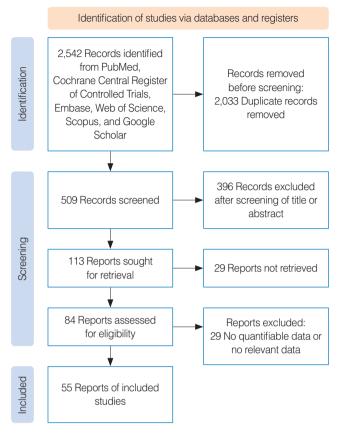


Fig. 1. Flow diagram of the selection of studies for analysis.

[25,34,35,38,39,41,43-47,50,51,61]. The risk of bias (methodological quality) was assessed using the Newcastle–Ottawa scale.

Statistical analyses

Meta-analyses were conducted in R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). When the extracted data were continuous, meta-analyses were performed using the standardized mean difference (SMD). As there are no standardized scales for evaluating the percentage or absolute count of eosinophils, total nonspecific IgE, endoscopic polyp score, symptom score, olfactory function, or CT score, we used this method to calculate effect sizes. All other analyses were OR analyses of the incidences of outcomes.

Heterogeneity was calculated with the I² test: The I² test describes the rate of variation across studies because of heterogeneity rather than probabilistic chance; the measure ranges from 0 (no heterogeneity) to 100 (maximum heterogeneity). All results are reported with 95% confidence interval (95% CI), and all *P*-values were two-tailed. When significant heterogeneity among outcomes was found (defined as I² >50), the random-effects model, according to DerSimonian-Laird, was used. This model assumes that the true treatment effects in individual studies may be different from one another, and that these are nor-

mally distributed. Those outcomes that did not present a significant level of heterogeneity ($I^2 < 50$) were analyzed with the fixed-effects model. The fixed-effects model uses the inverse variance approach, and it is assumed that all studies come from a common population. In addition, Subgroup analyses were done as a means of investigating heterogeneous results, which involve splitting all the participant data into subgroups in order to make comparisons between them. Subgroup analyses were done for subsets of different diagnostic criteria (such as tissue eosinophilia and clinicoradiological or laboratory characteristics), and for subsets of cutoff values (such as ≥ 10 eosinophils/ HPF, \geq 70 eosinophils/HPF, or \geq 10% eosinophils/total infiltrating cells. Sensitivity analyses were performed to determine the effects of individual studies on the overall meta-analysis results. We used a funnel plot and Egger's test simultaneously to detect publication bias. The trim-and-fill method also was done to indicate the significance of publication bias as well as provide biasadjusted results.

RESULTS

Search and study selection

In total, 55 studies with 6,143 participants were included in the meta-analysis. The characteristics, diagnostic criteria, and outcomes of the studies included in the analysis are summarized in Table 1. Many studies targeted only patients with CRS with nasal polyps. The diagnostic criteria were $\geq 10\%$ eosinophils/total infiltrating cells in 16 studies, ≥ 70 eosinophils/HPF in 15 studies, the JESREC score in 12 studies, and ≥ 10 eosinophils/HPF in 12 studies. The outcomes were CT scores in 40 studies, total non-specific IgE in 20 studies, percentage or absolute count of eosinophils in 18 studies, nasal symptomatic scores in 15 studies, and olfactory function in 10 studies. The quality (risk of bias) assessment of the studies is summarized in Supplementary Table 1.

Comparison of laboratory, clinical, and radiological findings between ECRS and non-ECRS

Several different diagnostic criteria and cutoff values were used to classify ECRS, including tissue eosinophilia (≥ 10 eosinophils/ HPF, ≥ 70 eosinophils/HPF, or $\geq 10\%$ eosinophils/total infiltrating cells) and the clinicoradiological laboratory score (JESREC score ≥ 11). The common clinical symptoms of ECRS may vary according to the diagnostic criteria used. A subgroup analysis of diagnostic criteria (clinicoradiological or laboratory characteristics) showed no significant differences in nasal symptom scores or CT scores (P > 0.05) among the four diagnostic criteria. However, there were significant differences in the serum percentage and count of eosinophils (P < 0.05) and olfactory dysfunction (P < 0.05). In post hoc analyses, serum eosinophil levels were significantly higher in ECRS than in non-ECRS for all diagnostic

11 Tospective 14 $42.\pm 13.3$ 66.28 Japan 100 270 Eosnophils/HF 14 Retrospective 15 $41.50(32.25-49.25)$ NR China 100 270 Eosnophils/HF 2 Retrospective 15 $450(32.75)$ 81.43 29.20 China 100 270.5 Eosnophils/HF 2 Retrospective 15 $450(32.25-49.25)$ NR China 100 270.5 Eosnophils/HF 2 Retrospective 55 $15-65$ 31.24 China 100 270.5 Eosnophils/HF 2 Retrospective 81 49 ± 15 NR Koraa 100 270.6 Eosnophils/HF 3 Retrospective 17 $352(475.63.5)$ 89.40 China 100 270.6 Eosnophils/HF 3 Retrospective 17 $52(475.63.5)$ 89.40 China 100 270.6 Eosnophils/HF 3 Retrospective 17 $82.62(37-3.49.0)$ NR 270.6 Eosnophils/HF 3	First author (year)	Study design	Number	Age (yr)	Sex (male:female)	Nation	Nasal polvp (%)	Diagnostic criteria	Outcome
[4] Rerospective 124 (16-30(5.7)) 81:43 Uspan 100 USSRECsome 2)[53] Consesectional 51 415.0(32.25-49.25) NR China 100 JUS Esenophils/her 0) Consesectional 69 53.7(22-74) NR China NR 20.55 esenophils/her 0) Consesectional 49 55.0(20-54.0) 29.32 7.22-74 Australia NR 20.55 esenophils/her 0) Consesectional 49 55.0(20-54.0) 29.32 7.22-74 Australia NR 20.55 esonophils/her 0) Consesectional 49 55.0(20-54.0) 29.32 7.22-74 NR 20.55 esonophils/her 10 Consesectional 49 55.0(20-54.0) 29.32 20.65 esonophils/her 11 Retrospective 51 49.515 NR 20.55 esonophils/her 15] Retrospective 53 52.4456.1 2.12 2.05 Esonophils/her 15] Retrospective 53 55.4456.1 <td>Nakayama (2011) [52]</td> <td>Prospective</td> <td>114</td> <td>48.2±13.3</td> <td>86:28</td> <td>Japan</td> <td>100</td> <td>≥70 Eosinophils/HPF</td> <td>IgE (IU/mL), CT score, nasal polyp score, nasal symptom score</td>	Nakayama (2011) [52]	Prospective	114	48.2±13.3	86:28	Japan	100	≥70 Eosinophils/HPF	IgE (IU/mL), CT score, nasal polyp score, nasal symptom score
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	Hu (2012) [3]	Retrospective	155	41.50 (32.25-49.25)	RN	China	100	≥10% Eosinophils/total infiltrating cells	Serum IgE, blood eosinophils, CT score, nasal polyp score, nasal symptom score
(1) Cross-sectional 49 55.7(2.7.4) NR Japan NR JESREC score 1 Cross-sectional 49 35.0(2054.0) 29.20 China 100 210% Ecsinophils/local 1 Retrospective 55 15-65 31.24 China 100 210% Ecsinophils/local 1 Retrospective 81 49±15 NR Korea 100 210% Ecsinophils/local 1 Retrospective 13 49±15 NR Korea 100 210% Ecsinophils/local 1 Retrospective 35 50.4(26-69) 25:14 1180:56 210% Ecsinophils/local 1 Retrospective 35 50.4(26-69) 25:14 100 210% Ecsinophils/local 2 Retrospective 35 50.4(26-69) 25:14 100 210% Ecsinophils/local 1 Retrospective 35 50.4(27-6) 30.4 100 210% Ecsinophils/local 1 Retrospective 35 60.2/7-49.0 17.8	Snidvongs (2012) [55]	Cross-sectional	51	46.6±4.1		Australia	RN	≥ 10 Eosinophils/HPF	CT score, nasal polyp score, nasal symptom score
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Retrospective 81 49 ± 15 NR Korea 100 210% Ecsimophils/hotal 1 Retrospective 128 $435(24.75-53.5)$ $88/40$ China 100 210% Ecsimophils/hotal 3)[5] Retrospective 176 52.4 ± 61.1 $1,180.536$ Japan 778 270 Eosimophils/hPF [53] Retrospective 5 $50.4(28-69)$ $25:14$ Japan 778 270 Eosimophils/hPF [53] Retrospective 5 $50.4(28-69)$ $25:14$ Japan 778 270 Eosimophils/hPF [51] Retrospective 5 $50.4(28-69)$ $25:14$ Japan 778 270 Eosimophils/hPF [53] Retrospective 5 $50.4(28-69)$ $23:14$ Japan 700 210% Eosimophils/hPF [51] Prospective 53 47.2 ± 15.2 $36:17$ 100 210% Eosimophils/hPF [51] Cross-sectional 34 $72.42-76)$ $30:4$ 470% Eosimophils/hPF [51] Prospective </td <td>Lin (2014) [57]</td> <td>Retrospective</td> <td>55</td> <td>15-65</td> <td>31:24</td> <td>China</td> <td>100</td> <td>>10% Eosinophils/total infiltrating cells</td> <td>CT score, nasal polyp score, nasal symptom score</td>	Lin (2014) [57]	Retrospective	55	15-65	31:24	China	100	>10% Eosinophils/total infiltrating cells	CT score, nasal polyp score, nasal symptom score
I Retrospective 128 43.5 (2.4.75-5.3.5) 88/40 China 100 210% Escinophils/hota 5)[5] Retrospective 1,716 5.2.4±6.1 1,180:536 Japan 77.8 270% Escinophils/hota [53] Retrospective 35 50.4 (26-69) 257.4 Japan 77.8 270 Escinophils/HF [53] Retrospective 35 50.4 (25-69) 257.4 Japan 77.8 270% Escinophils/het [31] Prospective 20 45.1±13.7 123.77 China 100 210% Escinophils/het 9] retrospective 53 47.2±15.2 30.4 Japan 100 270 Escinophils/het 9] retrospective 53 47.2±15.2 30.4 Japan 100 270 Escinophils/het 9] retrospective 53 47.2±15.2 30.4 Japan 100 270 Escinophils/het 11[15] retrospective 53 47.2±15.2 30.4 Japan 100 270 Escinophils/het	Kim (2015) [11]	Retrospective	81	49土15	RN	Korea	100	≥10% Eosinophils/total infiltrating cells	CT score, blood eosinophils
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	Tokunaga (2015) [5]	Retrospective	1,716	52.4±6.1	1,180:536	Japan	77.8	≥70 Eosinophils/HPF	Blood eosinophils
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[3] Cross-sectional 30 503±4.4 17:13 Japan 100 ≥70 Eosinophils/HF 9] retrospective 53 47.2±15.2 36:17 Turkey NR ≥10 Eosinophils/HF 4] Cross-sectional 34 58.3(42-76) 30:4 Japan 100 ≥70 Eosinophils/HF 1[15] Prospective 55 56.1(23-74) 40:16 Japan NR JESREC score 1[15] Retrospective 55 56.1(23-74) 40:16 Japan NR JESREC score 1[15] Retrospective 63 16-80 NR India 100 ≥70 Eosinophils/HF 0[17)[17] Retrospective 65 44.5 (25-71) 43:23 China 100 ≥10 Eosinophils/HF 017)[17] Retrospective 66 44.5 (25-71) 43:23 China 100 ≥10 Eosinophils/HF 017)[17] Retrospective 63 48.45 ±14.34 192:153 Australia 46.7 ≥10 Eosinophils/HF 010	Meng (2016) [12]	Prospective	200	45.1±13.7	123:77	China	100	≥10% Eosinophils/total infiltrating cells	CT score, blood eosinophils
9] retrospective 53 47.2±15.2 36:17 Turkey NR ≥10 Eosimophils/HPF 4] Cross-sectional 34 58.3(42-76) 30.4 Japan 100 ≥70 Eosimophils/HPF 1(15] Prospective 45 53.9±12.2 34:11 Japan NR JESREC score 1(15] Retrospective 56 56.1(23-74) 40:16 Japan NR JESREC score 16] Retrospective 56 56.1(23-74) 40:16 Japan NR JESREC score 16] Retrospective 63 44.5(25-71) 43:23 China 100 ≥70 Eosinophils/HPF 017) [17] Retrospective 66 44.5(25-71) 43:23 China 100 ≥70 Eosinophils/HPF 017) [17] Prospective 63 48.45±14.34 192:153 Australia 46.7 ≥10 Eosinophils/HPF 017) [17] Cross-sectional 24 57.5±13.5 33:31 Japan NR JeSREC score 01 <td< td=""><td>Tojima (2016) [13]</td><td>Cross-sectional</td><td>30</td><td>50.9±4.4</td><td>17:13</td><td>Japan</td><td>100</td><td>≥70 Eosinophils/HPF</td><td>CT score, IgE (IU/mL), blood eosinophils</td></td<>	Tojima (2016) [13]	Cross-sectional	30	50.9±4.4	17:13	Japan	100	≥70 Eosinophils/HPF	CT score, IgE (IU/mL), blood eosinophils
4] Cross-sectional 34 58.3 (42-76) 30.4 Japan 100 \geq 70 Eosinophils/HPF 1[15] Prospective 45 53.9 ± 12.2 34:11 Japan NR JESREC score 1[15] Retrospective 56 56.1 (23-74) 40:16 Japan 80.3 \geq 70 Eosinophils/HPF 017) I17 Retrospective 56 56.1 (23-74) 40:16 Japan NR JESREC score 16] Retrospective 66 44.5 (25-71) 43:23 China 100 \geq 10 Eosinophils/HPF 017) I17 Prospective 66 44.5 (25-71) 43:23 China 100 \geq 10 Eosinophils/HPF 64) Cross-sectional 345 48.45 \pm 14.34 192:153 Japan NR \geq 10 Eosinophils/HPF 61) Retrospective 64 57.5 \pm 13.5 33:31 Japan NR \geq 70 Eosinophils/HPF 61) Retrospective 64 57.5 \pm 13.5 33:31 Japan NR \geq 70	Aslan (2017) [59]	retrospective	53	47.2±15.2	36:17	Turkey	NR	≥ 10 Eosinophils/HPF	CT score, nasal polyp score
(15] Prospective 45 53.9±12.2 34:11 Japan NR JESREC score (16) Retrospective 56 56.1(23-74) 40:16 Japan 80.3 ≥70 Eosinophils/HPF 017) 171 Retrospective 56 56.1(23-74) 40:16 Japan 80.3 ≥70 Eosinophils/HPF 017) Tospective 63 16-80 NR India 100 ≥10% Eosinophils/HPF 017) Tospective 66 44.5 (25-71) 43:23 China 100 ≥10% Eosinophils/HPF 017) Prospective 66 44.5 (25-71) 43:23 China 100 ≥10% Eosinophils/HPF 64) Cross-sectional 345 48.45±14.34 192:153 Australia 46.7 ≥10 Eosinophils/HPF 61) Retrospective 64 57.5±13.5 33:31 Japan NR JESREC score 01 Cross-sectional 141 54.0±14.8 99:42 Japan NR 270 Eosinophils/HPF 18)	Baba (2017) [14]	Cross-sectional	34	58.3 (42–76)	30:4	Japan	100	≥70 Eosinophils/HPF	CT score, blood eosinophils
[16] Retrospective 56 56.1 (23-74) 40:16 Japan 80.3 ≥70 Eosinophils/HPF 017) [17] Retrospective 63 16–80 NR India 100 ≥10% Eosinophils/HPF 017) Prospective 63 16–80 NR India 100 ≥10% Eosinophils/HPF Retrospective 66 44.5 (25-71) 43:23 China 100 ≥10% Eosinophils/HPF 61 Cross-sectional 345 48.45 ±14.34 192:153 Australia 66.7 ≥10 Eosinophils/HPF 61 Rotrospective 64 57.5 ±13.5 33:31 Japan NR >70 Eosinophils/HPF 61 Retrospective 64 57.5 ±13.5 33:31 Japan NR >70 Eosinophils/HPF 61 Retrospective 64 57.5 ±13.5 33:31 Japan NR >70 Eosinophils/HPF 61 Cross-sectional 141 54.0 ±14.8 99:42 Japan NR >70 Eosinophils/HPF 70	Kambara (2017) [15]	Prospective	45	53.9±12.2	34:11	Japan	NR	JESREC score	Blood eosinophils, IgE (IU/mL)
017) IT Retrospective 63 16–80 NR India 100 ≥ 10 Eosinophils/HPF Prospective 66 44.5 (25-71) 43:23 China 100 ≥ 10% Eosinophils/hotal Respective 66 44.5 (25-71) 43:23 China 100 ≥ 10% Eosinophils/hotal S41 Cross-sectional 345 48.45 ± 14.34 192:153 Australia 46.7 ≥ 10 Eosinophils/HPF S41 Cross-sectional 22 52.7 ± 18.6 17:5 Japan 100 ≥70 Eosinophils/HPF 01 Retrospective 64 57.5 ± 13.5 33:31 Japan NR >70 Eosinophils/HPF 1271 Cross-sectional 141 54.0 ± 14.8 99:42 Japan NR >70 Eosinophils/HPF 181 [22] Retrospective 49 49.5 (78-18) 31:18 Japan NR >70 Eosinophils/HPF 181 [22] Prospective 21 45.0 ± 14.1 111:10 Korea 100 Japan NR </td <td>Kubota (2017) [16]</td> <td>Retrospective</td> <td>56</td> <td>56.1 (23–74)</td> <td>40:16</td> <td>Japan</td> <td>80.3</td> <td>≥70 Eosinophils/HPF</td> <td>CT score, blood eosinophils, IgE (IU/mL)</td>	Kubota (2017) [16]	Retrospective	56	56.1 (23–74)	40:16	Japan	80.3	≥70 Eosinophils/HPF	CT score, blood eosinophils, IgE (IU/mL)
Prospective 66 44.5 (25-71) 43:23 China 100 ≥10% Eosinophils/hotal 641 Cross-sectional 345 48.45±14.34 192:153 Australia 46.7 ≥10% Eosinophils/hPF 641 Cross-sectional 345 48.45±14.34 192:153 Australia 46.7 ≥10 Eosinophils/HPF 641 Cross-sectional 121 Cross-sectional 141 54.0±14.8 99:42 Japan NR JESREC score 01 Retrospective 49 49.5 (78-18) 31:18 Japan NR ≥70 Eosinophils/HPF 18) [22] Retrospective 49 49.5 (78-18) 31:18 Japan NR ≥70 Eosinophils/HPF 18) [22] Retrospective 21 45.0±14.1 11:10 Korea 100 JESREC score 23] Prospective 21 45.0±14.1 11:10 Korea 100 JESREC score 23] Prospective 8 56.2 (18-87) 44:24 Japan NR	Sreeparvathi (2017) [17]	Retrospective	63	16–80	NR	India	100	≥10 Eosinophils/HPF	Blood eosinophils
Cross-sectional 345 48.45±14.34 192:153 Australia 46.7 ≥ 10 Eosinophils/HPF 64] Cross-sectional 22 52.7±18.6 17:5 Japan 100 >70 Eosinophils/HPF 0] Retrospective 64 57.5±13.5 33:31 Japan 100 >70 Eosinophils/HPF 0] Retrospective 64 57.5±13.5 33:31 Japan NR JESREC score 1)[21] Cross-sectional 141 54.0±14.8 99:42 Japan NR >70 Eosinophils/HPF 18) [22] Retrospective 49 49.5 (78-18) 31:18 Japan NR >70 Eosinophils/HPF 18) [22] Prospective 21 45.0±14.1 11:10 Korea 100 JESREC score 200 cohort 21 45.0±14.1 11:10 Korea 100 JESREC score 21 bohort 21 45.0±14.1 11:10 Korea 100 JESREC score 21 Botoscore 23	Xu (2017) [18]	Prospective	66	44.5 (25–71)	43:23	China	100	≥10% Eosinophils/total infiltrating cells	Blood eosinophils
54] Cross-sectional 22 52.7 ± 18.6 17.5 Japan 100 ≥70 Eosinophils/HPF (0) Retrospective 64 57.5 ± 13.5 33.31 Japan NR JESREC score (1) Cross-sectional 141 54.0 ± 14.8 99:42 Japan NR JESREC score (21) Cross-sectional 141 54.0 ± 14.8 99:42 Japan NR ≥70 Eosinophils/HPF (1) Prospective 49 49.5 (78-18) 31:18 Japan NR ≥70 Eosinophils/HPF (23) Prospective 21 45.0 ± 14.1 11:10 Korea 100 JESREC score (23) Prospective 68 56.2 (18-87) 44:24 Japan 100 JESREC score (25) Retrospective 35 34.1 (18-40) 22:13 Japan NR >70 Eosinophils/HPF (26) Ferrospective 35 34.1 (18-40) 22:13 Japan NR >70 Eosinophils/HPF (27) 53	Ho (2018) [19]	Cross-sectional	345	48.45 ± 14.34		Australia	46.7	≥ 10 Eosinophils/HPF	Blood eosinophils, IgE (IU/mL)
0] Retrospective 64 57.5±13.5 33:31 Japan NR JESREC score 1[21] Cross-sectional 141 54.0±14.8 99:42 Japan NR ≥70 Eosinophils/HPF 18) [22] Retrospective 49 49.5 (78-18) 31:18 Japan NR ≥70 Eosinophils/HPF 18) [22] Prospective 21 45.0±14.1 11:10 Korea 100 JESREC score 23] Prospective 21 45.0±14.1 11:10 Korea 100 JESREC score 23] Prospective 68 56.2 (18-87) 44:24 Japan 100 JESREC score 9) [25] Retrospective 35 34.1 (18-40) 22:13 Japan NR ≥70 Eosinophils/HPF Procondition 134 53.41.60) 21.13 Japan NR ≥70 Eosinophils/HPF	Okada (2018) [54]	Cross-sectional	22	52.7 ± 18.6	17:5	Japan	100	≥70 Eosinophils/HPF	IgE (IU/mL), CT score, nasal polyp score
[21] Cross-sectional 141 54.0±14.8 99:42 Japan NR ≥70 Eosinophils/HPF 18) [22] Retrospective 49 49.5 (78-18) 31:18 Japan NR ≥70 Eosinophils/HPF 18) [22] Prospective 21 49.5 (78-18) 31:18 Japan NR ≥70 Eosinophils/HPF 23] Prospective 21 45.0±14.1 11:10 Korea 100 JESREC score 20 cohort 68 56.2 (18-87) 44:24 Japan 100 JESREC score 9) [25] Retrospective 35 34.1 (18-40) 22:13 Japan NR ≥70 Eosinophils/HPF Betrospective 134 53.41.60) 11.73 Kross 100 JESREC score	Tsuda (2018) [20]	Retrospective	64	57.5 ± 13.5	33:31	Japan	NR	JESREC score	Blood eosinophils
 [8] [22] Retrospective 49 49.5 (78-18) 31:18 Japan NR ≥70 Eosinophils/HPF [23] Prospective 21 45.0±14.1 11:10 Korea 100 JESREC score cohort Retrospective 68 56.2 (18-87) 44:24 Japan 100 JESREC score 9) [25] Retrospective 35 34.1 (18-40) 22:13 Japan NR ≥70 Eosinophils/HPF 	Uraguchi (2018) [21]	Cross-sectional	141	54.0±14.8	99:42	Japan	RN	≥70 Eosinophils/HPF	Blood eosinophils, CT score, IgE (IU/mL)
23 Prospective 21 45.0±14.1 11:10 Korea 100 JESREC score cohort cohort 44.24 Japan 100 JESREC score Retrospective 68 56.2 (18-87) 44:24 Japan 100 JESREC score 9) [25] Retrospective 35 34.1 (18-40) 22:13 Japan NR ≥70 Eosinophils/HPF Detrospective 124 53.4.1 (18-40) 11.73 Knoos 100 IESREC score	Wakayama (2018) [22]	Retrospective	49	49.5 (78–18)	31:18	Japan	NR	≥70 Eosinophils/HPF	Blood eosinophils, IgE (IU/mL)
Retrospective 68 56.2 (18-87) 44:24 Japan 100 JESREC score 9) [25] Retrospective 35 34.1 (18-40) 22:13 Japan NR >70 Eosinophils/HPF Patrospective 134 53.4.1 (18-0) 111-93 Knoos 100 IESREC score	Hwang (2019) [23]	Prospective cohort	21	45.0±14.1	11:10	Korea	100	JESREC score	Blood eosinophils, CT score, IgE (IU/mL), olfactory function
9) [25] Retrospective 35 34.1 (18-40) 22:13 Japan NR ≥70 Eosinophils/HPF Performantive 134 53.741.60) 111-03 Korea 100 IESBEC some	lto (2019) [24]	Retrospective	68	56.2 (18-87)	44:24	Japan	100	JESREC score	Blood eosinophils, CT score
Batrosonactiva 13/ 53 (/1_60) 111.03 Koraa 100 IESBED soora	Kashiwagi (2019) [25]	Retrospective	35	34.1 (18–40)	22:13	Japan	RN	≥70 Eosinophils/HPF	Blood eosinophils, CT score, olfactory function
heliospecilye 134 33 (41-00) 111,23 Notea 100 JESHEV SQUE	Kim (2019) [26]	Retrospective	134	53 (41–60)	111:23	Korea	100	JESREC score	Blood eosinophils, CT score, olfactory function

Table 1. Characteristics, diagnostic criteria, and outcomes of the studies included in the analysis

Table 1. Continued

First author (year)	Study design	Number	Age (yr)	Sex (male:female)	Nation	Nasal polvn (%)	Diagnostic criteria	Outcome
Liu (2019) [27]	Prospective	48	46.6±14.8	29:19	China	100	≥10% Eosinophils/total infiltrating cells	Blood eosinophils, olfactory function
Nakayama (2019) [28]	Cross-sectional	29	53.2±16.0	23:6	Japan	100	JESREC score	Blood eosinophils, CT score, nasal polyp score
Shen (2019) [29]	Prospective	100	46.78±16.13	72:28	Taiwan	100	≥ 10 Eosinophils/HPF	Blood eosinophils, CT score, nasal polyp score
Tsuzuki (2019) [30]	Retrospective	281	52.1±13.5 (21–79)	171:110	Japan	NR	JESREC score	Blood eosinophils, IgE (IU/mL), CT score, nasal polyp score, olfactory function
Wang (2019) [31]	Retrospective	120	42.3±6.4	65:55	China	NR	≥ 10 Eosinophils/HPF	Blood eosinophils, CT score, total symptom score
Yoshida (2019) [32]	Prospective	103	50.2±2.6	NR	Japan	NR	≥70 Eosinophils/HPF	Blood eosinophils, CT score, nasal polyp score
Fadda (2020) [33]	Retrospective	110	49.8±15.2	74:36	Italy	100	≥10 Eosinophils/HPF	Blood eosinophils, CT score, nasal polyp score, nasal symptom score
Imoto (2020) [34]	Cross-sectional	72	54.7±13.6	53:19	Japan	100	≥70 Eosinophils/HPF	Blood eosinophils
Ky (2020) [9]	Prospective	83	ЧN	48:35	Vietnam	100	≥ 10 Eosinophils/HPF	Blood eosinophils, CT score, nasal polyp score
Lv (2020) [35]	Cross-sectional	20	42.6±15.6	43:27	China	100	≥10% Eosinophils/total infiltrating cells	Blood eosinophils, CT score, IgE (IU/mL)
Sivrice (2020) [36]	Prospective	299	45.43±14.92	179:120	Turkey	100	≥10% Eosinophils/total infiltrating cells	Blood eosinophils
Xu (2020) [37]	Retrospective	66	40.6±12.1	62:37	China	100	≥10% Eosinophils/total infiltrating cells	Blood eosinophils, CT score, nasal polyp score, nasal symptom score, olfactory function
Yao (2020) [38]	Cross-sectional	30	44.5 (38–50.75)	24:6	China	100	>10% Eosinophils/total infiltrating cells	CT score, nasal polyp score
Yun (2020) [39]	Cross-sectional	20	58.7 ± 10.2	12:8	Japan	09	> 70 Eosinophils/HPF	Blood eosinophils, IgE (IU/mL)
Zhu (2020) [40]	Prospective	86	46.0 (35.5–57.0)	62:24	China	100	≥10% Eosinophils/total infiltrating cells	Blood eosinophils, CT score, IgE (IU/mL), nasal symptom score
Zhu (2020) [41]	Cross-sectional	82	46 (52–50)	RN	China	100	≥10% Eosinophils/total infiltrating cells	Blood eosinophils, nasal polyp score, CT score, IgE (IU/mL), olfactory function, nasal symptom score
Ahn (2020) [42]	Retrospective	224	50.6 ± 13.5	153:71	Korea	70.1	JESREC score	Olfactory function
Abbas (2020) [43]	Cross-sectional	46	34.69 ± 16.39	20:26	Sudan	100	≥10 Eosinophils/HPF	Blood eosinophils, CT score, nasal polyp score
Feng (2020) [45]	Cross-sectional	34	39.16	18:16	China	100	≥ 10% Eosinophils/total infiltrating cells	Blood eosinophils, CT score, nasal symptom score
Kawasumi (2021) [45]	Cross-sectional	45	NR	21:24	Japan	NR	≥70 Eosinophils/HPF	Blood eosinophils, CT score
Kowalik (2021) [46]	Cross-sectional	96	48.8	60:36	Poland	56.3	≥10 Eosinophils/HPF	Nasal symptom score
Rha (2021) [47]	Retrospective	53	47 (40.3–56)	40:13	Korea	100	≥70 Eosinophils/HPF	CT score
Takahashi (2021) [48]	Retrospective	56	62.3±13.8	18:38	Japan	NR	JESREC score	Blood eosinophils, IgE (IU/mL), CT score, olfactory function
Terada (2021) [49]	Prospective	37	51 (34–63)	12:25	Japan	NR	JESREC score	Blood eosinophils
Wang (2021) [50]	Cross-sectional	32	50 (24.26-66.25)	25:7	China	100	≥10 Eosinophils/HPF	CT score, nasal symptom score
Zhong (2021) [51]	Retrospective	65	42.79±6.11	37:28	China	100	≥10 Eosinophils/HPF	Blood eosinophils, CT score, nasal polyp score, nasal
								symptom score
Values are presented as mean \pm standard deviation, median (range), or range.	mean±standard de	eviation, m	edian (range), or range					

cant (0.587 [95% CI, -0.227 to 1.401]). In laboratory findings, the eosinophil percentage (SMD=1.561 [95% CI, 1.329–1.794], *P*<0.001, Cochrane Q=3 41.30, *P*<0.001, I²=89.5%), eosinophil count (SMD=1.493 [95% CI, 1.134–1.852], *P*<0.001, Cochrane Q=327.33, *P*<0.001, I²=93.0%), and total IgE (SMD=0.359 [95% CI, 0.118–0.600], *P*=0.004, Cochrane Q=69.54, *P*<0.001, I²=77.0%) were significantly higher in ECRS than in non-ECRS (Fig. 2). Regarding the clinical findings, nasal symptom scores (SMD=0.382 [95% CI, 0.156–0.608], *P*=0.0009,

tory function, although the effects were not statistically signifi-

Cochrane Q=65.86, P<0.001, I²=75.7%), olfactory dysfunction (SMD=0.416 [95% CI, 0.037-0.794], P=0.031, Cochrane Q=86.62, P < 0.001, $I^2 = 88.5\%$), and endoscopic nasal polyp scores (SMD= 0.581 [95% CI, 0.314–0.848], P<0.001, Cochrane Q=124.01, P < 0.001, I²=83.9%) were significantly higher in ECRS than in non-ECRS (Fig. 3). As a radiological finding, the whole-sinus opacification score (SMD=0.824 [95% CI. 0.588-1.059], P< 0.0001, Cochrane Q=368.13, P<0.001, I²=88.9%) was significantly higher in ECRS than in non-ECRS (Fig. 4). In particular, anterior ethmoid sinus (SMD=0.535 [95% CI, 0.351-0.720], Cochrane Q=3.89, P=0.421, $I^2=0.0\%$) and sphenoid sinus (SMD=0.431 [95% CI, 0.143-0.718], Cochrane Q=8.98, P= $0.062, I^2 = 55.5\%$) opacification was significantly higher in ECRS than in non-ECRS (Supplementary Fig. 1). However, there were no significant differences in the frontal sinus (SMD=0.385 [95% CI, -0.065 to 0.835], Cochrane Q=30.42, P<0.001, I²=83.6%),

Study To	tal I	Experii Nean		Total	Mean	Control SD	Standardised Mean Difference	SMD	95%-CI	Weight (fixed)	Weigh (random
g = > 10 eosinophils/HPF Ho 2018	206	6.210	4.4800	139	2.500	1.8400		1.013 [0.785	: 1.2411	7.9%	3.4%
Shen 2019	59		3.3700			1.8800		0.844 [0.428		2.4%	3.29
Fadda 2020	65		4.2000			3.3000		0.618 [0.229		2.7%	3.29
Abbas 2021	32		7.7500			1.0000	<u>⊢++</u> ;	-	1.322]	1.0%	2.89
Fixed effect model	362			239			6	0.884 [0.712		14.0%	
Random effects model							ă	0.866 [0.673			12.5
Heterogeneity: $l^2 = 13\%$, $\tau^2 = 0$.	.0057, (p = 0.33						01000 [01010	, 11000]		1210
g = > 70 eosinophils/HPF Tokunaga 2015	672	7 4 2 0	5.5400	1044	0.000	3,7400		0 700 10 000	0.0201	41.1%	3.5
								0.730 [0.630			
Tojima 2016 Kubota 2017	14 36		0.8000 4.9750	16 20	3.000	1.3000 1.9750			; 3.892] ; 1.900]	0.4%	2.0
Baba 2017	17		0.5500			0.5250				0.1%	0.8
								8.535 [6.275]			
Uraguchi 2018	53		4.9000			2.0000	18	1.472 [0.969		1.6%	3.0
Uraguchi 2018	58		3.1000			2.0000	15.		; 1.842]	1.7%	3.0
Okuda 2018	12		2.7000			1.3000			; 3.414]	0.3%	1.9
Wakayama 2018	24		3.5100			3.5600	~ {	0.946 [0.353		1.2%	2.9
Kachiwagi 2019	17		1.7500			0.7550			; 1.090]	0.1%	2.1
Kashiwagi 2019	17		0.5500	18		0.4600			; 9.047]	0.1%	1.1
Yoshida 2019	25		0.8000			0.3000		8.163 [6.688		0.2%	1.5
Imoto 2020	48		4.7000			1.4000			; 1.498]	1.5%	3.0
Kawasumi 2021 Fixed effect model	27 1020	7.500	3.5000	18 1315	2.800	2.5000		1.469 [0.793 0.912 [0.822		0.9%	2.7
Random effects model	1020			1010			! *⇔		: 3.362]	30.070	30.3
Heterogeneity: $l^2 = 95\%$, $\tau^2 = 1$.	4194, j	0 < 0.01					→ → → + + + + + + + + +	2.000 [1.903	; 3.302]		30.3
g = >10% eosinophils/tota	al infi	trating	cells								
Hu 2012	66	4.900	2.9650	89	1.800	1.3710	持	1.406 [1.050	; 1.761]	3.2%	3.2
Meng 2016	123	7.580	3.5000	77	4.790	3.0000	=	0.838 [0.541	; 1.135]	4.7%	3.3
Xu 2017	30	19.920	9.1900	36	4.970	2.2200	i + -	2.308 [1.676	; 2.941]	1.0%	2.8
Nakayama 2019	42	9.000	4.4000	9	2.600	1.5000	++-	1.548 [0.763	; 2.333]	0.7%	2.5
Liu 2019	31	6.300	2.2970	17	2.800	2.2010	 	1.521 [0.849	; 2.192]	0.9%	2.7
Wang 2019	68	6.400	3.2990	47	2.400	1.5780	i i	1.454 [1.036	; 1.872]	2.3%	3.2
Wang 2019	84	5.900	2.7420	30	3.000	2.0000	+{	1.121 [0.678	; 1.563]	2.1%	3.1
Zhu 2020	65	5.600	2.8910	21	2.300	2.4460	- 1	1.172 [0.648	1.695]	1.5%	3.0
Lv 2020	24	5.200	3,4000	46	3,100	2.2000		0.779 0.268	1.290]	1.6%	3.0
Zhu 2020	43	3.800	2.5200			2.8160			0.7331	2.2%	3.1
Xu 2020	49		3.2700	50		2.8800		•	1.249]	2.4%	3.2
Feng 2021	16		3,7000	18		1.4700	 		2.419]	0.7%	2.5
Fixed effect model	641			479			6:		1.239]	23.3%	
Random effects model							l de		1.4701		35.6
Heterogeneity: $l^2 = 75\%$, $\tau^2 = 0$.	1668, j	p < 0.01									
g = JESREC score											
Sakuma 2011	62	11.100	5.1000	62	1.100	3.8000		1.426 [1.031	; 1.8221	2.6%	3.2
Takeno 2013	33	8.500	4.0000	16	2.700	2.1750	++-		2.305]	0.9%	2.7
Kambara 2017	23		2.9000			2.3000	<u> -</u>		2.7091	0.8%	2.6
Hwang 2019			3.4000			1.4000	1:		4.3781	0.2%	1.6
Ito 2019	38		4.0100			1.4300		1.639 [1.083		1.3%	2.9
Nakavama 2019	20		2.7000			1.5000	_ 	1.171 [0.320		0.6%	2.4
Tsuzuki 2019	205		4.4000			1.3000	<u> </u>		1.968	4.6%	3.3
Takahashi 2021	18		4.6000	38		4.1000	분		; 1.760]	1.1%	2.8
Fixed effect model	410	3.700	4.0000	263	4.700	4.1000	10		; 1.769]	12.2%	2.0
Random effects model	410			200			16	1.586 [1.351		6 E.+E /0	21.6
Heterogeneity: $l^2 = 27\%$, $\tau^2 = 0$.	.0294, j	p = 0.21						1.500 [1.551	, 1.021]		21.0
Fixed effect model	2433			2296				1.035 [0.971	; 1.0991	100.0%	
Random effects model							· •	1.561 [1.329			100.0
								Lunger Lunger			
Heterogeneity: 1 ² = 89%, τ ² = 0.	4010	p < 0.01									

Fig. 2. Forest plot. (A) Percentage of eosinophils in eosinophilic and non-eosinophilic chronic rhinosinusitis.

(Continued to the next page)

		Exper	imental		Co	ntrol	Standardised Mean			Weight	Weig
Study	Total	Mean	SD To	otal	Mean	SD	Difference	SMD	95%-Cl	-	(randor
g = > 10 eosinophils/HF Sreeparvatathi 2017	PF 33	10.900	3.8000	30	3.600	1.9000		2 365	[1.712; 3.018]	1.9%	4.1
Brescia 2017	45		0.4200	70	0.210	0.1600			[0.530; 1.317]	5.3%	4.5
Aslan 2017	33			20	0.100	0.1000	1 <u>1</u>		[0.966; 2.246]	2.0%	4.2
Ho 2018	206			139	0.100	0.1300	+		[0.927; 1.391]	15.1%	4.7
Shen 2019	59	359.730	304.9900	41	178.000	177.7800		0.692	[0.281, 1.102]	4.8%	4.5
Ky 2020	28			55	249.800			0.842	[0.368; 1.316]	3.6%	4.4
Fadda 2020	65		0.5000	45	0.300	0.2000			[0.152; 0.926]	5.4%	4.5
Abbas 2021	32			14	0.160	0.0700	1		[-0.134; 1.140]	2.0%	4.2
Kowalik 2021	68			28	0.150	0.1950	i in		[0.595; 1.527]	3.8%	4.4
Zhong 2021 Fixed offect model	30 599		0.2700	35 477	0.300	0.2200	i.		[1.381; 2.583]	2.3% 46.2%	4.2
Fixed effect model Random effects model Heterogeneity: 1 ² = 79%, τ ² =				411					[0.925; 1.191] [0.821; 1.434]	40.2%	43.9
g = > 70 eosinophils/HF		p < 0.01									
Imoto 2020		420 100	331.6000	24	156.800	102 2000		0.937	[0.422; 1.452]	3.1%	4.
Yun 2020			192.6000		245.500		+ 		[-0.230; 1.623]	0.9%	3.0
Fixed effect model	60			32				0.880	[0.430; 1.330]	4.0%	
Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 =$		86					4	0.880	[0.430; 1.330]	-	8.
g = >10% eosinophils/to	total infi	iltrating o	ells								
Hu 2012	66	0.310	0.1700	89	0.100	0.0810		1.649	[1.281; 2.018]	6.0%	4.
Kim 2015	36	156.100	112.7000	45	121.900	120.7000		0.289	[-0.152; 0.730]	4.2%	4.
Meng 2016	123	0.110	0.2800	77	0.330	0.2300		0.118	[0.131; 0.706]	9.8%	4.
Lv 2020	24		0.2000	46	0.190	0.1600			[0.227; 1.246]	3.1%	4.
Zhu 2020	43		0.1400	39	0.100	0.1334			[0.414; 1.323]	4.0%	4.
Sivrice 2020	197			102	0.240	0.2100	*: + *		[0.323; 0.810]	13.8%	4.
Feng 2021	16		0.2400	18	0.080	0.0800	0		[0.835; 2.413]	1.3%	3.
Fixed effect model Random effects model	505			416			8		[0.593; 0.871] [0.460; 1.219]	42.2%	31.
Heterogeneity: $I^2 = 85\%$, $\tau^2 =$		p < 0.01					* * *	0.040	[0.400, 1.215]		51.
g = JESREC score											
Kambara 2017		529.300			185.700	28.2000			[6.603; 10.478]	0.2%	2
Tsuda 2018			346.1000		220.800		走		[0.826; 1.924]	2.7%	4.
Ito 2019		400.000		30	116.000	97.0000		1.607	[1.053; 2.160]	2.7%	4.
Kim 2019 Terada 2021	77	363.000 552.000		57 25	116.000 234.000	20.0000 33.0000		5.012 6.506	[4.314; 5.711]	1.7% 0.3%	4.
Fixed effect model	184		70.0000	164	234.000	33.0000			[4.794; 8.219] [2.330; 2.989]	7.5%	۷.
Random effects model				104					[2.363; 6.520]	1.0/0	17.
Heterogeneity: $I^2 = 97\%$, $\tau^2 =$									[riccol clored]		
Heterogeneity: 1 = 37%, 2 =	= 5.2440,	p < 0.01									
				4020			6	4 024	10044 4 4241	400.0%	
Fixed effect model	1348			1089			6 •		[0.944; 1.124] [1.134: 1.852]	100.0%	100.0
Fixed effect model Random effects model Heterogeneity: $l^2 = 93\%$, $\tau^2 =$	1348 el = 0.6981,	p < 0.01		1089		-10		1.493	[0.944; 1.124] [1.134; 1.852]	100.0% 	100.0
Fixed effect model Random effects mode	1348 el = 0.6981,	p < 0.01		1089		-10	∲: 			100.0% 	100.
Fixed effect model Random effects mode Heterogeneity: $l^2 = 93\%$, $\tau^2 = 9$ Residual heterogeneity: $l^2 = 9$	1348 el = 0.6981, 91%, <i>p</i> <	<i>p</i> < 0.01 0.01 Exper	imental			ntrol	-5 0 5 Standardised Mean	1.49 3 10	[1.134; 1.852]	Weight	Weig
Fixed effect model Random effects model Heterogeneity: $l^2 = 93\%, \tau^2 = 93\%$ Residual heterogeneity: $l^2 = 9$ Study	1348 = 0.6981, 91%, <i>p</i> <	p < 0.01 0.01	imental SD To		Cc Mean		-5 0 5 Standardised Mean Difference	1.493			Wei
Fixed effect model Random effects mode Heterogeneity: / ² = \$3%, τ ² = Residual heterogeneity: / ² = \$ Study g = > 10 cosinophils/HP	1348 = 0.6981, 91%, <i>p</i> < Total	<i>p</i> < 0.01 0.01 Exper Mean	SD To	otal	Mean	ontrol SD	-5 0 5 Standardised Mean	1.493 10 SMD	[1.134; 1.852] 95%-Cl	 Weight (fixed)	Weig (rando
Fixed effect model Random effects model Heterogeneity: $l^2 = 93\%, \tau^2$ Residual heterogeneity: $l^2 = 9$ Study g = > 10 cosinophils/HP Ho 2018	1348 = 0.6981, 91%, <i>p</i> < Total	<i>p</i> < 0.01 0.01 Exper	SD To	otal 139		ntrol	-5 0 5 Standardised Mean Difference	1.493 10 SMD 0.123	[1.134; 1.852] 95%-Cl 3 [-0.092; 0.339]	 Weight (fixed) 23.4%	Weig (rando
Fixed effect model Random effects model Heterogeneity: / ² = 93%, z ² = Residual heterogeneity: / ² = 9 Study g = > 10 eosinophils/HP Ho 2018 Fixed effect model	1348 = 0.6981, 91%, p < Total PF 206 206	<i>p</i> < 0.01 0.01 Exper Mean	SD To	otal	Mean	ontrol SD	-5 0 5 Standardised Mean Difference	1.493 10 SMD 0.12: 0.12:	[1.134; 1.852] 95%-Cl 3 [-0.092; 0.339] 3 [-0.092; 0.339]	 Weight (fixed)	Weig (rando 8.
Fixed effect model Random effects model Heterogeneity: $l^2 = 93\%, \tau^2$ Residual heterogeneity: $l^2 = 9$ Study g = > 10 cosinophils/HP Ho 2018	1348 = 0.6981, 91%, <i>p</i> < Total PF 206 206	<i>p</i> < 0.01 0.01 Exper Mean	SD To	otal 139	Mean	ontrol SD	-5 0 5 Standardised Mean Difference	1.493 10 SMD 0.12: 0.12:	[1.134; 1.852] 95%-Cl 3 [-0.092; 0.339]	 Weight (fixed) 23.4%	Wei (rando 8.
Fixed effect model Random effects model Heterogeneity: / ² = \$3%, z ² = Residual heterogeneity: / ² = \$ Study g = > 10 eosinophils/HP Ho 2018 Fixed effect model Random effects model Heterogeneity: not applicable	1348 el = 0.6981, 91%, p < Total PF 206 206	<i>p</i> < 0.01 0.01 Exper Mean	SD To	otal 139	Mean	ontrol SD	-5 0 5 Standardised Mean Difference	1.493 10 SMD 0.12: 0.12:	[1.134; 1.852] 95%-Cl 3 [-0.092; 0.339] 3 [-0.092; 0.339]	 Weight (fixed) 23.4%	Wei (rando 8
Fixed effect model Random effects model Heterogeneity: / ² = 93%, ² = Residual heterogeneity: / ² = 9 Study g = > 10 eosinophils/HP Ho 2018 Fixed effect model Random effects model	1348 el = 0.6981, 91%, p < Total 206 206 I 206	<i>p</i> < 0.01 0.01 Exper Mean	SD To	otal 139	Mean	ontrol SD	-5 0 5 Standardised Mean Difference	1.493 10 SMD 0.12: 0.12: 0.12:	(1.134; 1.852) 95%-Cl 3 [-0.092; 0.339] 3 [-0.092; 0.339]	 Weight (fixed) 23.4%	Wei (rando 8. 8
Fixed effect model Random effects model Heterogeneity: / ² = 93%, ² = Residual heterogeneity: / ² = 9 Study g = > 10 eosinophils/HP Ho 2018 Fixed effect model Random effects model Heterogeneity: not applicable g = > 70 eosinophils/HP	1348 1 1 1 1 1 1 1 1	p < 0.01 0.01 Exper Mean 182.310	SD To 293.9300	otal 139 139	Mean 146.640	ntrol SD 280.7200	-5 0 5 Standardised Mean Difference	1.493 10 SMD 0.123 0.123 0.123	95%-Cl -0.092; 0.339] -0.092; 0.339] -0.092; 0.339]	 Weight (fixed) 23.4% 23.4%	Wei (rando 8 8 7.
Fixed effect model Random effects model Heterogeneity: J ² = 93%, τ ² Residual heterogeneity: J ² = 9 Study g = > 10 eosinophils/HP Ho 2018 Fixed effect model Random effects model Heterogeneity: not applicable g = > 70 eosinophils/HP Nakayama 2011	1348 = 0.6981, 91%, p < Total PF 206 206 1 PF 68 14	p < 0.01 0.01 Exper Mean 182.310 277.600	SD To 293.9300 364.6000	139 139 139 46	Mean 146.640 178.900	280.7200 358.8000 55.0000 19.5000	-5 0 5 Standardised Mean Difference	1.493 10 SMD 0.12: 0.12: 0.12: 0.12: 0.12: 0.12: 0.12: 0.12:	95%-Cl 95%-Cl 3 [-0.092; 0.339] 3 [-0.092; 0.339] 3 [-0.092; 0.339] 1 [-0.105; 0.646]	 Weight (fixed) 23.4% 7.7%	Wei (rando 8 8 7 4
Fixed effect model Random effects model Heterogeneity: $l^2 = 93\%$, $\tau^2 = 8$ Residual heterogeneity: $l^2 = 9$ Study g = > 10 cosinophils/HP Ho 2018 Fixed effect model Random effects model Heterogeneity: not applicable g = > 70 cosinophils/HP Nakayama 2011 Tojima 2016 Kouzaki 2016 Kouzaki 2017	1348 = 0.6981, 91%, p < Total DF 206 206 1 206 1 5 68 14 17 36	p < 0.01 0.01 Exper Mean 182.310 277.600 217.000 327.900	SD To 293.9300 364.6000 37.0000 31.1000 922.8500	139 139 46 16 18 20	Mean 146.640 178.900 192.000 132.500 424.500	280.7200 358.8000 55.0000 19.5000 938.5000	-5 0 5 Standardised Mean Difference	1.493 10 SMD 0.12:	95%-Cl 95%-Cl 3 [-0.092; 0.339] 3 [-0.092; 0.339] 3 [-0.092; 0.339] 4 [-0.105; 0.646] 2 [-0.219; 1.243] 5 [5.446; 9.362] 5 [-0.429; 0.565]	 Weight (fixed) 23.4% 23.4% 7.7% 2.0% 0.3% 3.6%	Wei (rando 8 8 7 7 4 6
Fixed effect model Random effects model Heterogeneity: / ² = 93%, ² = Residual heterogeneity: / ² = 9 Study g = > 10 eosinophils/HP Ho 2018 Fixed effect model Random effects model Heterogeneity: not applicable g = > 70 eosinophils/HP Nakayama 2011 Tojima 2016 Kouzaki 2016 Kubota 2017 Uraguchi 2018	1348 = 0.6981, 91%, p < Total 206 1 206 1 206 1 206 1 206 1 206 3 206 1 206 3 206 1 206 3 206 3 206 3 206 3 206 3 2 3 3 3 3 3 3 3 3 3 3 3 3 3	p < 0.01 0.01 Exper Mean 182.310 277.600 217.000 327.900 441.400 214.000	SD To 293.9300 364.6000 37.0000 31.1000 922.8500 338.0000	139 139 46 16 16 20 30	Mean 146.640 178.900 192.000 132.500 424.500 130.000	280.7200 358.8000 55.0000 19.5000 938.5000 111.0000	-5 0 5 Standardised Mean Difference	1.493 10 SMD 0.122 0.123	95%-Cl 95%-Cl 3 [-0.092; 0.339] 3 [-0.092; 0.339] 3 [-0.092; 0.339] 4 [-0.105; 0.646] 2 [-0.219; 1.243] 5 [5.448; 9.362] 3 [-0.529; 0.565] 5 [-0.148; 0.738]	 (fixed) 23.4% 23.4% 7.7% 2.0% 0.3% 3.6% 5.5%	Wei (rando 8 8 7 4 1 6 6
Fixed effect model Random effects model Heterogeneity: J ² = 93%, z ² = Residual heterogeneity: J ² = 9 Study g = > 10 eosinophils/HP Ho 2018 Fixed effect model Reandom effects model Heterogeneity: not applicable g = > 70 eosinophils/HP Nakayama 2011 Tojima 2016 Kuuzaki 2016 Kuuzaki 2017 Uraguchi 2018 Okuda 2018	1348 = 0.6981, 91%, p < Total 206 206 1 206 1 206 1 206 1 206 1 206 206 1 2 2 1 2 2 1 1 1 1 1 1 1 1 1 1 1 1 1	p < 0.01 0.01 Exper Mean 182.310 277.600 217.000 327.900 441.400 214.000 253.200	SD To 293.9300 364.6000 37.0000 31.1000 922.8500 338.0000 236.1000	139 139 46 16 18 20 30 10	Mean 146.640 178.900 192.000 132.500 424.500 130.000 109.400	358.8000 55.0000 938.5000 938.5000 111.0000	-5 0 5 Standardised Mean Difference	1.493 10 SMD 0.122 0.122 0.122 0.122 0.122 0.122 0.122 0.122 0.122 0.122 0.122 0.122	95%-Cl 95%-Cl 3 [-0.092; 0.339] 3 [-0.092; 0.339] 3 [-0.092; 0.339] 1 [-0.219; 1.243] 5 [5.448; 9.362] 3 [-0.529; 0.565] 5 [-0.148; 0.738] 9 [-0.148; 1.600]	 Weight (fixed) 23.4% 23.4% 7.7% 2.0% 0.3% 0.3% 5.5% 1.4%	Wei (rando 8 8 7 4 1 6 6 4 4
Fixed effect model Random effects mode Heterogeneity: / ² = 93%, - ² = Residual heterogeneity: / ² = 9 Study g = > 10 cosinophils/HP Ho 2018 Fixed effect model Random effects model Heterogeneity: not applicable g = > 70 cosinophils/HP Nakayama 2011 Kuuzaki 2016 Kuuzaki 2017 Uraguchi 2018 Okuda 2018 Vakayama 2018	1348 = 0.6981, 91%, 9 Total DF 206 206 1 DF 68 14 17 36 58 12 24	p < 0.01 0.01 Exper Mean 182.310 277.600 217.000 327.900 441.400 253.200 179.460	SD To 293.9300 364.6000 37.0000 31.1000 922.8500 338.0000 236.1000 240.2400	139 139 46 16 18 20 30 10 25	Mean 146.640 178.900 192.000 132.500 424.500 130.000 109.400 189.590	358.8000 55.0000 19.5000 938.5000 111.0000 1223.4500	-5 0 5 Standardised Mean Difference	1.493 10 SMD 0.122 0.122 0.122 0.122 0.122 0.122 0.122 0.512 0.512 0.014 0.299 0.072 0.721	95%-Cl 95%-Cl 3 [-0.092; 0.339] 3 [-0.092; 0.339] 3 [-0.092; 0.339] 3 [-0.092; 0.339] 4 [-0.105; 0.646] 2 [-0.219; 1.243] 5 [-5.446; 9.3662] 5 [-0.219; 0.565] 5 [-0.144; 1.600] 5 [-0.144; 1.600] 5 [-0.144; 1.600]	 Weight (fixed) 23.4% 23.4% 7.7% 2.0% 0.3% 3.6% 5.5% 1.4% 3.5%	Wei (rando 8 8 7. 4 1. 6 6 6 4 4 4
Fixed effect model Random effects model Heterogeneity: $I^2 = 93\%, \tau^2 = 93\%$ Residual heterogeneity: $I^2 = 93\%$ Study g = > 10 eosinophils/HP Ho 2018 Fixed effect model Random effects model Heterogeneity: not applicable g = > 70 eosinophils/HP Nakayama 2011 Tojima 2016 Kuubta 2017 Uraguchi 2018 Okuda 2018 Wakayama 2018 Yun 2020	1348 = 0.6981, 91%, p < Total PF 206 206 1 207 68 14 17 36 58 12 24 24	p < 0.01 0.01 Exper Mean 182.310 277.600 217.000 327.900 441.400 253.200 179.460	SD To 293.9300 364.6000 37.0000 31.1000 922.8500 338.0000 236.1000	139 139 46 16 18 20 30 10 25 8	Mean 146.640 178.900 192.000 132.500 424.500 130.000 109.400 189.590	358.8000 55.0000 938.5000 938.5000 111.0000	-5 0 5 Standardised Mean Difference	1.493 10 SMD 0.12;	95%-Cl 95%-Cl 1.0.092; 0.339] 1.0.092; 0.339] 3.0.092; 0.350] 3.0.092; 0.350] 3.002; 0.002; 0.350] 3.002; 0.		Wei (rando 8 8 7 4 1 6 6 6 4 4 6
Fixed effect model Random effects model Heterogeneity: / ² = 93%, ² = Residual heterogeneity: / ² = 9 Study g = > 10 eosinophils/HP Ho 2018 Fixed effect model Random effects model Heterogeneity: not applicable g = > 70 eosinophils/HP Nakayama 2011 Tojima 2016 Kouzaki 2016 Kubota 2017 Uraguchi 2018 Okuda 2018 Wakayama 2018 Yun 2020 Fixed effect model Random effects model	1348 = 0.6981, 91%, p < Total 206 206 1 26 1 26 1 26 1 26 1 26 1 26 1 26 206 206 206 206 206 206 206	p < 0.01 0.01 Exper Mean 182.310 277.600 217.000 327.900 414.000 253.200 179.460 761.200	SD To 293.9300 364.6000 37.0000 31.1000 922.8500 338.0000 236.1000 240.2400	139 139 46 16 18 20 30 10 25	Mean 146.640 178.900 192.000 132.500 424.500 130.000 109.400 189.590	358.8000 55.0000 19.5000 938.5000 111.0000 1223.4500	-5 0 5 Standardised Mean Difference	1.493 10 SMD 0.12: 0.01: 0.02: 0.01: 0.02:	95%-Cl 95%-Cl 3 [-0.092; 0.339] 3 [-0.092; 0.339] 3 [-0.092; 0.339] 3 [-0.092; 0.339] 4 [-0.105; 0.646] 2 [-0.219; 1.243] 5 [-5.446; 9.3662] 5 [-0.219; 0.565] 5 [-0.144; 1.600] 5 [-0.144; 1.600] 5 [-0.144; 1.600]		Wei (rand 8 8 7 4 1 6 6 4 4 6 4 4 4
Fixed effect model Random effects model Heterogeneity: / ² = 93%, z ² = Residual heterogeneity: / ² = 9 Study g = > 10 eosinophils/HP Ho 2018 Fixed effect model Random effects model Heterogeneity: not applicable g = > 70 eosinophils/HP Nakayama 2011 Tojima 2016 Kouzaki 2016 Kubota 2017 Uraguchi 2018 Okuda 2018 Wakayama 2018 Yun 2020 Fixed effect model	1348 = 0.6981, 91%, p < Total 206 206 1 26 1 26 1 26 1 26 1 26 1 26 1 26 206 206 206 206 206 206 206	p < 0.01 0.01 Exper Mean 182.310 277.600 217.000 327.900 414.000 253.200 179.460 761.200	SD To 293.9300 364.6000 37.0000 31.1000 922.8500 338.0000 236.1000 240.2400	139 139 46 16 18 20 30 10 25 8	Mean 146.640 178.900 192.000 132.500 424.500 130.000 109.400 189.590	358.8000 55.0000 19.5000 938.5000 111.0000 1223.4500	-5 0 5 Standardised Mean Difference	1.493 10 SMD 0.12: 0.01: 0.02: 0.01: 0.02:	95%-Cl 95%-Cl 3 [-0.092; 0.339] 3 [-0.092; 0.339] 3 [-0.092; 0.339] 4 [-0.105; 0.646] 2 [-0.219; 1.243] 5 [-5.446; 9.362] 3 [-0.259; 0.565] 5 [-0.148; 0.738] 9 [-0.148; 0.738] 1 [-0.603; 0.517] 7 [-0.546; 1.260] 9 [-0.149; 0.533]		Wei (rand 8 8 7 4 1 6 6 4 4 6 4 4 4
Fixed effect model Random effects model Heterogeneity: $I^2 = 93\%$, $\tau^2 = 82\%$ Residual heterogeneity: $I^2 = 93\%$ Study g = > 10 eosinophils/HP Ho 2018 Fixed effect model Random effects model Heterogeneity: not applicable g = > 70 eosinophils/HP Nakayama 2011 Tojima 2016 Kubota 2017 Uraguchi 2016 Kubota 2017 Uraguchi 2018 Okuda 2018 Vuraguchi 2018 Vuraguchi 2018 Yun 2020 Fixed effect model Random effects model Heterogeneity: $I^2 = 87\%$, $\tau^2 = g = >10\%$ eosinophils/to	1348 = 0.6981, 91%, p < Total 206 206 206 1 26 1 26 1 26 1 26 1 26 1 26 1 206 206 206 206 206 206 206 206	p < 0.01 0.01 Exper Mean 182.310 277.600 217.000 327.900 441.400 253.200 179.460 761.200 p < 0.01 trating c	SD To 293.9300 364.6000 37.0000 31.1000 922.8500 338.0000 236.1000 240.2400 1332.8000	139 139 46 16 18 20 30 10 25 8	Mean 146.640 178.900 192.000 132.500 424.500 130.000 199.400 189.500 358.500	358.8000 55.0000 19.5000 938.5000 111.0000 110.3000 223.4500 461.7000	-5 0 5 Standardised Mean Difference	1.493 10 SMD 0.12;	95%-Cl 95%-Cl 3 [-0.092; 0.339] 3 [-0.092; 0.339] 3 [-0.092; 0.339] 3 [-0.092; 0.339] 4 [-0.105; 0.646] 2 [-0.219; 1.243] 5 [5.448; 9.362] 5 [-0.144; 0.738] 3 [-0.144; 1.600] 5 [-0.144; 1.600] 5 [-0.144; 1.600] 5 [-0.149; 0.533] 2 [0.107; 1.357]		Wei (rand) 8 8 8 7 4 1 1 6 6 4 4 4 4 4 4 40
Fixed effect model Random effects mode Heterogeneity: $l^2 = 93\%$, $z^2 = 823\%$ Residual heterogeneity: $l^2 = 93\%$ Study g = > 10 cosinophils/HP Ho 2018 Fixed effect model Random effects model Heterogeneity: not applicable g = > 70 cosinophils/HP Nakayama 2011 Tojima 2016 Kouzaki 2016 Kuuzaki 2016 Kuuzaki 2017 Uraguchi 2018 Okuda 2017 Uraguchi 2018 Okuda 2018 Yun 2020 Fixed effect model Random effects model Heterogeneity: $l^2 = 87\%$, $z^2 =$	1348 = 0.6981, 91%, p < Total 206 206 206 1 26 1 26 1 26 1 26 1 26 1 26 1 206 206 206 206 206 206 206 206	p < 0.01 0.01 Exper Mean 182.310 277.600 217.000 327.900 179.460 761.200 r < 0.01 trating cc	SD To 293.9300 364.6000 37.0000 31.1000 922.8500 338.0000 236.1000 240.2400 1332.8000	139 139 139 46 16 18 20 30 10 25 8 173	Mean 146.640 178.900 192.000 132.500 424.500 130.000 109.400 189.590	358.8000 55.0000 19.5000 938.5000 111.0000 1223.4500	-5 0 5 Standardised Mean Difference	1.493 10 SMD 0.12;	95%-Cl 95%-Cl 3 [-0.092; 0.339] 3 [-0.092; 0.339] 3 [-0.092; 0.339] 4 [-0.105; 0.646] 2 [-0.219; 1.243] 5 [-5.446; 9.362] 3 [-0.259; 0.565] 5 [-0.148; 0.738] 9 [-0.148; 0.738] 1 [-0.603; 0.517] 7 [-0.546; 1.260] 9 [-0.149; 0.533]		Wei (rando 8 8 7 4 4 6 6 4 6 4 4 40 7 7
Fixed effect model Random effects mode Heterogeneity: $l^2 = 53\%$, $\tau^2 = 83\%$ Residual heterogeneity: $l^2 = 53\%$ Study g = > 10 cosinophils/HP Ho 2018 Fixed effect model Random effects model Heterogeneity: not applicable g = > 70 cosinophils/HP Nakayama 2011 Tojima 2016 Kouzaki 2016 Kuubata 2017 Uraguchi 2018 Okuda 2018 Wakayama 2018 Yun 2020 Fixed effect model Random effects model Heterogeneity: $l^2 = 87\%$, $\tau^2 = 37\%$	1348 = 0.6981, 91%, p < Total PF 206 206 1 26 1 26 1 26 1 26 1 26 1 26 26 26 26 26 20 26 20 20 20 20 20 20 20 20 20 20	p < 0.01 0.01 Exper Mean 182.310 277.600 217.000 327.900 179.460 761.200 r < 0.01 trating cc	SD To 293.9300 364.6000 37.0000 31.1000 922.8500 338.0000 240.2400 1332.8000	139 139 46 16 18 30 10 25 8 173	Mean 146.640 178.900 192.000 132.500 424.500 130.000 199.400 189.590 358.500 16.550 72.800	280.7200 280.7200 358.8000 55.0000 19.5000 938.5000 110.3000 223.4500 461.7000	-5 0 5 Standardised Mean Difference	1.493 10 SMD 0.12; 0.01; 0.01; 0.01; 0.01; 0.01; 0.02;	95%-Cl 95%-Cl 1.134; 1.852] 95%-Cl 3. [-0.092; 0.339] 3. [-0.092; 0.339] 3. [-0.092; 0.339] 4. [-0.219; 1.243] 5. [-0.48; 9.362] 5. [-0.48; 9.362] 3. [-0.603; 0.517] 7. [-0.546; 1.260] 5. [-0.148; 0.733] 2. [-0.17; 1.357] 2. [-0.189; 0.836]	 Weight (fixed) 23.4% 23.4% 2.0% 0.3% 3.6% 1.4% 3.5% 1.3% 25.4% 1.3% 25.4%	Wei (rando 8 8 8 7 4 4 10 6 6 6 6 4 4 4 0 7 7 6
Fixed effect model Random effects mode Heterogeneity: $l^2 = 93\%$, $z^2 = 83\%$ Residual heterogeneity: $l^2 = 93\%$ Study g = > 10 cosinophils/HP Ho 2018 Fixed effect model Random effects model Heterogeneity: not applicable g = > 70 cosinophils/HP Nakayama 2011 Tojima 2016 Kouzaki 2016 Kubota 2017 Uraguchi 2018 Okuda 2018 Vun 2020 Fixed effect model Random effects model Heterogeneity: $l^2 = 87\%$, $z^2 = 97\%$ g = >10% cosinophils/tc Hu 2012 Zhu 2020 Lv 2020 Fixed effect model	1348 = 0.6981, 91%, p < Total PF 206 206 1 26 1 26 1 26 1 26 1 26 1 26 24 12 241 1 0.6509, p otal infil 65 24 155	p < 0.01 0.01 Exper Mean 182.310 277.600 217.000 327.900 441.400 253.200 179.460 761.200 p < 0.01 traing ct 105.000 68.100	SD To 293.9300 364.6000 37.0000 31.1000 922.8500 338.0000 240.2400 1332.8000	139 139 139 46 16 18 20 30 130 25 8 173 89 21	Mean 146.640 178.900 192.000 132.500 424.500 130.000 199.400 189.590 358.500 16.550 72.800	280.7200 358.8000 55.0000 19.5000 938.5000 111.0000 110.3000 223.4500 461.7000	-5 0 5 Standardised Mean Difference	1.493 10 SMD 0.12: 0.012: 0.012: 0.012: 0.012: 0.012: 0.012: 0.012: 0.012: 0.012: 0.02: 0.012: 0.02	95%-Cl 95%-Cl 3 [-0.092; 0.339] 3 [-0.092; 0.339] 3 [-0.092; 0.339] 3 [-0.092; 0.339] 4 [-0.105; 0.646] 2 [-0.219; 1.243] 5 [-5.446; 9.362] 5 [-0.219; 1.243] 5 [-0.259; 0.565] 5 [-0.148; 0.738] 9 [-0.148; 0.738] 9 [-0.148; 0.533] 2 [0.107; 1.357] 2 [0.189; 0.836] 5 [-0.538; 0.446] 0 [-0.176; 0.817] 3 [-0.176; 0.817] 3 [-0.176; 0.576]	 Weight (fixed) 23.4% 23.4% 2.0% 0.3% 3.6% 5.5% 1.4% 5.5% 1.3% 25.4% 10.4% 4.5% 4.4%	Wei (rando 8 8 8 8 8 8 7 4 4 1 6 6 6 4 4 4 0 7 7 6 6 6
Fixed effect model Random effects model Heterogeneity: $I^2 = 93\%$, $z^2 = 8$ Residual heterogeneity: $I^2 = 9$ Study g = > 10 cosinophils/HP Ho 2018 Fixed effect model Random effects model Heterogeneity: not applicable g = > 70 cosinophils/HP Nakayama 2011 Tojima 2016 Kouzaki 2016 Kubota 2017 Uraguchi 2018 Okuda 2018 Wakayama 2018 Yun 2020 Fixed effect model Random effects model Heterogeneity: $I^2 = 87\%$, $z^2 = 2$ g = >10% cosinophils/to Hu 2012 Zhu 2020 Ly 2020 Fixed effect model Random effects model Random effects model Random effects model Random effects model Random effects model	1348 = 0.6981, = 0.6981, 91%, p < Total 206 206 1 26 1 26 1 26 1 26 1 26 1 26 20 20 20 20 20 20 20 20 20 20	p < 0.01 0.01 Exper Mean 182.310 277.600 217.000 327.900 441.400 214.000 761.200 761.200 re < 0.01 trating ct 105.000 68.100 148.800	SD To 293.9300 364.6000 37.0000 31.1000 922.8500 338.0000 240.2400 1332.8000	139 139 139 46 16 18 20 30 30 10 25 8 173 89 21 46	Mean 146.640 178.900 192.000 132.500 424.500 130.000 199.400 189.590 358.500 16.550 72.800	280.7200 358.8000 55.0000 19.5000 938.5000 111.0000 110.3000 223.4500 461.7000	-5 0 5 Standardised Mean Difference	1.493 10 SMD 0.12: 0.012: 0.012: 0.012: 0.012: 0.012: 0.012: 0.012: 0.012: 0.012: 0.02: 0.012: 0.02	95%-Cl 95%-Cl [1.134; 1.852] 95%-Cl [-0.092; 0.339] [-0.092; 0.339] [-0.092; 0.339] [-0.092; 0.339] [-0.092; 0.339] [-0.092; 0.339] [-0.105; 0.646] [-0.219; 1.243] [-0.219; 1.243] [-0.529; 0.565] [-0.148; 0.738] [-0.483; 0.517] [-0.189; 0.836] [-0.189; 0.836] [-0.189; 0.836] [-0.538; 0.446] [-0.1817]	 Weight (fixed) 23.4% 23.4% 2.0% 0.3% 3.6% 5.5% 1.4% 5.5% 1.3% 25.4% 10.4% 4.5% 4.4%	Weii (rand) 8 8 8 8 8 8 7 4 4 1 6 6 6 4 4 4 0 7 7 6 6 6
Fixed effect model Random effects mode: Heterogeneity: $l^2 = 93\%$, $z^2 = 32\%$ Residual heterogeneity: $l^2 = 93\%$ Study g = > 10 cosinophils/HP Ho 2018 Fixed effect model Random effects model Heterogeneity: not applicable g = > 70 cosinophils/HP Nakayama 2011 Tojma 2016 Kuuzaki 2016 Kuuzaki 2016 Kuuzaki 2016 Kuuzaki 2017 Uraguchi 2018 Okuda 2018 Vun 2020 Fixed effect model Raterogeneity: $l^2 = 87\%$, $z^2 = 32\%$ Hu 2012 Zhu 2020 LV 2020 Fixed effect model Random effects model Random effects model Random effects model Random effects model	1348 = 0.6981, = 0.6981, 91%, p < Total 206 206 1 26 1 26 1 26 1 26 1 26 1 26 20 20 20 20 20 20 20 20 20 20	p < 0.01 0.01 Exper Mean 182.310 277.600 217.000 327.900 441.400 214.000 761.200 761.200 re < 0.01 trating ct 105.000 68.100 148.800	SD To 293.9300 364.6000 37.0000 31.1000 922.8500 338.0000 240.2400 1332.8000	139 139 139 46 16 18 20 30 30 10 25 8 173 89 21 46	Mean 146.640 178.900 192.000 132.500 424.500 130.000 199.400 189.590 358.500 16.550 72.800	280.7200 358.8000 55.0000 19.5000 938.5000 111.0000 110.3000 223.4500 461.7000	-5 0 5 Standardised Mean Difference	1.493 10 SMD 0.12: 0.012: 0.012: 0.012: 0.012: 0.012: 0.012: 0.012: 0.012: 0.012: 0.02: 0.012: 0.02	95%-Cl 95%-Cl 3 [-0.092; 0.339] 3 [-0.092; 0.339] 3 [-0.092; 0.339] 3 [-0.092; 0.339] 4 [-0.105; 0.646] 2 [-0.219; 1.243] 5 [-5.446; 9.362] 5 [-0.219; 1.243] 5 [-0.259; 0.565] 5 [-0.148; 0.738] 9 [-0.148; 0.738] 9 [-0.148; 0.533] 2 [0.107; 1.357] 2 [0.189; 0.836] 5 [-0.538; 0.446] 0 [-0.176; 0.817] 3 [-0.176; 0.817] 3 [-0.176; 0.576]	 Weight (fixed) 23.4% 23.4% 2.0% 0.3% 3.6% 5.5% 1.4% 5.5% 1.3% 25.4% 10.4% 4.5% 4.4%	Wei (rand- 8 8 7 4 4 6 6 6 4 4 4 6 4 4 6 7 6 6 6
Fixed effect model Random effects model Heterogeneity: $I^2 = 93\%$, $\tau^2 = 82\%$ Residual heterogeneity: $I^2 = 93\%$ Study g = > 10 cosinophils/HP Ho 2018 Fixed effect model Random effects model Heterogeneity: not applicable g = > 70 cosinophils/HP Nakayama 2011 Tojima 2016 Kubota 2017 Uraguchi 2016 Kubota 2017 Uraguchi 2018 Okuda 2018 Wakayama 2018 Yun 2020 Fixed effect model Heterogeneity: $I^2 = 87\%$, $\tau^2 = g = >10\%$ cosinophils/to Hu 2012 Zhu 2020 Li 2	1348 = 0.6981, 91%, p < Total PF 206 206 1 207 68 14 17 36 58 14 17 36 58 12 241 1 241 1 0 0.6509, j 0 0.0355, j 0 0.0055, j 0 0 0.0355, j 0 0.0355	p < 0.01 0.01 Exper Mean 182.310 277.600 217.000 327.900 441.400 217.000 253.200 179.460 761.200 c < 0.01 trating c: 105.000 68.100 148.800 p = 0.18	SD To 293.9300 364.6000 37.0000 31.1000 922.8500 338.0000 236.1000 240.2400 1332.8000	139 139 46 16 16 16 16 16 16 10 25 8 173 89 21 1 73 89 21 156	Mean 146.640 178.900 132.500 424.500 133.000 199.400 189.500 358.500 16.550 72.800 85.100	280.7200 280.7200 358.8000 55.0000 19.5000 938.5000 111.0000 110.3000 223.4500 461.7000	-5 0 5 Standardised Mean Difference	1.493 10 SMD 0.122 0.511 0.012 0.511 0.012 0.511 0.012 0.523 0.523 0.523 0.523 0.523 0.523 0.523 0.523 0.523 0.523 0.523 0.523 0.523 0.523 0.523 0.523 0.524 0.523 0.523 0.524 0.532 0.524 0.532 0.532 0.532 0.532 0.533	95%-Cl 95%-Cl 1.134; 1.852] 95%-Cl 1.[-0.092; 0.339] 1.[-0.092; 0.339] 1.[-0.092; 0.339] 1.[-0.092; 0.339] 1.[-0.092; 0.339] 1.[-0.105; 0.646] 2.[-0.219; 1.243] 1.[-0.105; 0.646] 2.[-0.219; 1.243] 1.[-0.105; 0.646] 3.[-0.529; 0.565] 3.[-0.148; 0.738] 3.[-0.603; 0.517] 3.[-0.603; 0.517] 3.[-0.603; 0.517] 2.[-0.189; 0.836] 3.[-0.538; 0.446] 3.[-0.538; 0.446] 3.[-0.538; 0.446] 3.[-0.538; 0.446] 3.[-0.538; 0.446] 3.[-0.104; 0.576] 3.[-0.024; 0.628]	 Weight (fixed) 23.4% 23.4% 23.4% 2.0% 0.3% 5.5% 1.4% 3.6% 5.5% 1.4% 25.4% 25.4% 10.4% 4.4% 19.2%	Wei (rando 8 8 8 8 8 8 8 7 7 4 1 1 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6
Fixed effect model Random effects mode Heterogeneity: $l^2 = 93\%$, $\tau^2 = 83\%$ Residual heterogeneity: $l^2 = 93\%$ Study g = > 10 cosinophils/HP Ho 2018 Fixed effect model Random effects model Heterogeneity: not applicable g = > 70 cosinophils/HP Nakayama 2011 Tojima 2016 Kouzaki 2016 Kubota 2017 Uraguchi 2018 Okuda 2018 Vuna 2011 Vakayama 2011 Sixed effect model Random effects model Heterogeneity: $l^2 = 87\%$, $\tau^2 = 97\%$ g = >10% cosinophils/tc Hu 2012 Zhu 2020 Fixed effect model Random effects model Heterogeneity: $l^2 = 42\%$, $\tau^2 = 97\%$ g = JESREC score Sakuma 2011	1348 = 0.6981, 91%, p < Total PF 206 206 1 26 1 26 1 26 1 26 1 26 1 26 1 26 1 26 1 26 1 206 206 1 206 206 1 206 206 1 206 206 1 206 206 1 206 206 1 206 206 1 206 206 1 206 206 1 206 206 1 206 206 1 206 206 1 206 206 1 206 206 1 206 206 1 206 206 1 206 206 1 206 206 1 207 1 206 206 1 206 206 1 207 1 206 206 1 207 1 207 1 207 1 2 2 2 2 2 2 2 2 2 2 2 2 2	p < 0.01 0.01 Exper Mean 182.310 277.600 217.000 327.900 441.400 253.200 r61.200 c < 0.01 trating c: 179.460 761.200 e < 0.01 trating c: 105.000 68.100 148.800 p = 0.18 302.000	SD To 293.9300 364.6000 37.0000 31.1000 922.8500 338.0000 236.1000 240.2400 1332.8000 240.2400 1332.8000	139 139 139 46 16 18 20 30 10 25 8 173 89 21 46 156	Mean 146.640 178.900 192.000 132.500 424.500 130.000 109.400 139.590 358.500 16.550 72.800 85.100 237.000	10000000000000000000000000000000000000	-5 0 5 Standardised Mean Difference	1.493 10 SMD 0.122 0.042 0.042 0.355 0.352 0.325 0.355	95%-Cl 95%-Cl 1.134; 1.852] 95%-Cl 3. [-0.092; 0.339] 3. [-0.092; 0.339] 3. [-0.092; 0.339] 3. [-0.092; 0.339] 3. [-0.092; 0.339] 3. [-0.092; 0.339] 5. [-0.219; 1.243] 5. [-0.546; 1.260] 5. [-0.148; 0.533] 2. [-0.176; 0.817] 3. [-0.176; 0.530] 7. [-0.176; 0.530]	 Weight (fixed) 23.4% 23.4% 2.0% 0.3% 3.6% 5.5% 1.4% 5.5% 1.3% 25.4% 1.3% 25.4% 1.3% 25.4% 1.3% 25.4% 1.3% 25.4% 1.3% 2.4% 2.4% 2.4% 2.4% 2.4% 2.4% 2.4% 2.4	Weii (rando 8 8 8 8 8 8 7 4 4 1 6 6 6 6 6 6 6 200 7 7
Fixed effect model Random effects model Heterogeneity: $l^2 = 93\%$, $z^2 = 32\%$ Residual heterogeneity: $l^2 = 93\%$ Study g = > 10 cosinophils/HP Ho 2018 Fixed effect model Random effects model Heterogeneity: not applicable g = > 70 cosinophils/HP Nakayama 2011 Tojma 2016 Kouzaki 2016 Kubota 2017 Uraguchi 2018 Okuda 2018 Vun 2020 Fixed effect model Random effects model Heterogeneity: $l^2 = 87\%$, $z^2 = 32$ g = >10% cosinophils/tc Hu 2020 Lv 2020 Lv 2020 Fixed effect model Random effects model Heterogeneity: $l^2 = 87\%$, $z^2 = 32$ g = >10% cosinophils/tc Hu 2020 Lv 2020 Lv 2020 Lv 2020 State offect model Random effects model Heterogeneity: $l^2 = 42\%$, $z^2 = 32\%$ g = JESREC score Sakuma 2017	1348 = 0.6981, = 0.6981, 91%, p < Total 206 206 1 206 1 206 1 206 1 206 206 1 206 206 1 206 206 1 206 206 1 206 206 1 206 206 1 224 1 1 2 241 1 1 5 24 1 5 24 1 1 5 24 1 1 5 24 1 1 5 24 1 5 24 1 5 24 1 5 24 1 5 24 1 5 2 2 2 2 2 2 2 2 2 2 2 2 2	p < 0.01 0.01 Exper Mean 182.310 277.600 217.000 327.900 441.400 253.200 761.200 p < 0.01 trating ct 105.000 68.100 148.800 p = 0.18 302.000 415.400	SD To 293.9300 364.6000 37.0000 31.1000 922.8500 338.0000 240.2400 1332.8000 1332.8000 1332.8000 100.1100 180.3000 293.0000 601.1000	0tal 139 139 46 16 18 20 30 105 8 173 89 21 46 156 62 22	Mean 146.640 178.900 192.000 132.500 424.500 130.000 130.000 139.500 358.500 16.550 72.800 85.100 237.000 247.600	49.0580 425.0000 425.0000 111.0000 111.0000 111.0000 110.0000 223.4500 461.7000	-5 0 5 Standardised Mean Difference	1.493 10 SMD 0.12; 0.01; 0.01; 0.01; 0.01; 0.01; 0.01; 0.01; 0.01; 0.01; 0.01; 0.02; 0.32;	95%-Cl 95%-Cl 3 [-0.092; 0.339] 3 [-0.092; 0.339] 3 [-0.092; 0.339] 3 [-0.092; 0.339] 3 [-0.092; 0.339] 4 [-0.105; 0.646] 5 [-0.219; 1.243] 5 [-5.448; 9.362] 5 [-0.148; 0.738] 3 [-0.144; 1.600] 5 [-0.148; 0.738] 3 [-0.144; 1.600] 5 [-0.148; 0.738] 5 [-0.148; 0.738] 5 [-0.148; 0.738] 5 [-0.148; 0.633] 5 [-0.176; 0.533] 5 [-0.246; 0.918] 5 [-0.260; 0.918	 Weight (fixed) 23.4% 23.4% 2.0% 0.3% 3.6% 5.5% 1.4% 3.5% 1.3% 25.4% 10.4% 4.5% 4.4% 19.2% 8.7% 3.1%	Wei (rando 8 8 8 8 8 8 8 7 7 6 6 6 6 6 6 6 7 7 6 20 7 5
Fixed effect model Random effects model Heterogeneity: $l^2 = 93\%$, $z^2 = 8$ Residual heterogeneity: $l^2 = 93\%$ Study g = > 10 cosinophils/HP Ho 2018 Fixed effect model Random effects model Heterogeneity: not applicable g = > 70 cosinophils/HP Nakayama 2011 Tojima 2016 Kuuzaki 2016 Kuuzaki 2016 Kuuzaki 2016 Kuuzaki 2017 Uraguchi 2018 Wakayama 2018 Wakayama 2018 Wakayama 2018 Wakayama 2018 Wakayama 2018 Wakayama 2018 Wakayama 2018 Usu 2020 Fixed effect model Random effects model Heterogeneity: $l^2 = 87\%$, $z^2 =$ g = >10% cosinophils/tc Hu 2012 Zhu 2020 Fixed effect model Random effects mo	1348 1 = 0.6981, 91%, p < Total PF 206 206 1 26 1 27 68 14 17 36 58 12 24 12 241 1 0.6509, j otal infill 66 65 24 155 1 0.0355, j 62 23 11	p < 0.01 0.01 Exper Mean 182.310 277.600 217.000 327.900 179.460 761.200 761.200 761.200 a < 0.01 trating cc 148.800 p = 0.18 302.000 415.400 234.600	SD To 293.9300 364.6000 37.0000 31.1000 922.8500 338.0000 240.2400 1332.8000 240.2400 1332.8000 240.2400 1332.8000 257.3700 100.1100 180.3000	139 139 46 16 18 20 30 0 10 25 8 9 21 173 89 21 156 62 22 210	Mean 146.640 178.900 192.000 192.500 424.500 139.590 358.500 16.550 72.800 85.100 237.000 247.600 47.000	425.0000 482.000	-5 0 5 Standardised Mean Difference	1.493 10 SMD 0.12; 0.35; 0.32; 0.33; 0.33; 0.30; 0.32; 0.32; 0.32; 0.33; 0.33; 0.30; 0.32; 0.32; 0.32; 0.33; 0.32; 0.32; 0.32; 0.32; 0.33; 0.32; 0.32; 0.32; 0.32; 0.33; 0.32; 0.52; 0.32; 0.32; 0.52; 0.32; 0.52; 0.32; 0.52; 0.32; 0.52;	95%-Cl 95%-Cl 1.134; 1.852] 95%-Cl 1.[-0.092; 0.339] 1.[-0.092; 0.339] 3.[-0.092; 0.339] 3.[-0.092; 0.339] 3.[-0.092; 0.339] 1.[-0.219; 1.243] 3.[-0.489; 3.62] 3.[-0.489; 3.62] 3.[-0.463; 0.738] 3.[-0.463; 0.738] 3.[-0.463; 0.738] 3.[-0.463; 0.738] 3.[-0.463; 0.738] 3.[-0.463; 0.738] 3.[-0.463; 0.738] 3.[-0.463; 0.738] 3.[-0.463; 0.738] 3.[-0.463; 0.486] 3.[-0.538; 0.446] 3.[-0.538; 0.446] 3.[-0.246; 0.628] 7.[-0.176; 0.530] 9.[-0.260; 0.918] 1.[-0.463; 0.547] 3.[-0.463; 0.548] 3.[-0.463; 0.5	 Weight (fixed) 23.4% 23.4% 23.4% 2.3.4% 2.3.4% 2.3.4% 3.6% 3.6% 2.5.4% 3.5% 2.5.4% 2.5.4% 2.5.4% 1.4% 4.4% 3.1% 3.1% 3.1%	Wei (rando 8 8 8 7 7 4 4 6 6 6 6 6 6 6 6 20 20 7 7 5 3 3
Fixed effect model Random effects mode: Heterogeneity: $l^2 = 93\%$, $z^2 = 8$ Residual heterogeneity: $l^2 = 93\%$, $z^2 = 93\%$, $z^2 = 93\%$, $z^2 = 93\%$ Study g = > 10 cosinophils/HP Ho 2018 Fixed effect model Random effects model Heterogeneity: not applicable g = > 70 cosinophils/HP Nakayama 2011 Tojma 2016 Kouzaki 2016 Kubota 2017 Uraguchi 2018 Okuda 2018 Vun 2020 Fixed effect model Random effects model Heterogeneity: $l^2 = 87\%$, $z^2 = 97\%$ Hu 2012 Zhu 2020 LV 2020 Fixed effect model Random effects model Rando	1348 = 0.6981, 91%, p < Total PF 206 206 1 26 1 26 1 26 1 26 1 26 1 26 1 26 1 26 1 26 1 26 1 26 1 26 1 26 26 1 26 26 1 26 26 1 26 26 26 26 26 26 26 26 26 26	p < 0.01 0.01 Exper Mean 182.310 277.600 217.000 327.900 441.400 2141.400 2141.400 2141.400 2141.400 761.200 p < 0.01 trating c 105.000 68.100 148.800 p = 0.18 302.000 415.400 234.600 342.100	SD To 293.9300 364.6000 37.0000 31.1000 922.8500 338.0000 236.1000 240.2400 1332.8000 1332.8000 100.1100 180.3000 601.1000 153.9000 574.8000	139 139 139 46 16 18 20 30 30 10 25 8 173 89 21 46 156 156 222 10 076	Mean 146.640 178.900 192.000 132.500 424.500 139.590 358.500 16.550 72.800 85.100 237.000 247.600 47.000 239.500	425.0000 425.0000 425.0000 425.0000 425.0000 425.0000 42000 425.0000 42000 425.0000 42000 42000	-5 0 5 Standardised Mean Difference	1.493 10 SMD 0.12: 0.04: 0.35: 0.32! 0.32! 0.32: 0.5: 0:	95%-Cl 95%-Cl 3 [-0.092; 0.339] 3 [-0.092; 0.339] 3 [-0.092; 0.339] 3 [-0.092; 0.339] 4 [-0.105; 0.646] 5 [-0.219; 1.243] 5 [.5.446; 9.366] 5 [-0.219; 1.243] 5 [.5.446; 9.366] 5 [-0.148; 0.738] 8 [-0.144; 1.600] 3 [-0.630; 0.517] 7 [-0.546; 1.260] 9 [-0.176; 0.533] 2 [0.107; 1.357] 2 [0.189; 0.836] 5 [-0.538; 0.446] 0 [-0.176; 0.817] 9 [-0.260; 0.918] 5 [-0.245; 0.545] 9 [-0.260; 0.918] 5 [-0.545; 2.547] 7 [-0.87; 0.440]	 Weight (fixed) 23.4% 23.4% 2.0% 0.3% 3.6% 5.5% 1.4% 3.5% 1.3% 25.4% 4.5% 4.4% 19.2% 4.5% 4.4% 19.2% 3.1% 1.1%	Wei (rando 8 8 8 8 8 8 8 7 7 4 4 1 6 6 6 6 6 6 6 20 20 7 7 5 3 8 8
Fixed effect model Random effects model Heterogeneity: $I^2 = 93\%$, $\tau^2 = 8$ Residual heterogeneity: $I^2 = 9$ Study g = > 10 eosinophils/HP Ho 2018 Fixed effect model Random effects model Heterogeneity: not applicable g = > 70 eosinophils/HP Nakayama 2011 Tojima 2016 Kubota 2017 Uraguchi 2018 Okuda 2018 Vuraguchi 2018 Okuda 2017 Uraguchi 2018 Okuda 2018 Vura 020 Fixed effect model Random effects model Heterogeneity: $I^2 = 87\%$, $\tau^2 =$ g =>10% eosinophils/to Hu 2020 Lv 2020	1348 = 0.6981, 91%, p < Total PF 206 206 1 26 1 26 1 26 1 26 1 26 1 26 1 26 1 26 1 26 1 26 1 26 1 26 1 26 26 1 26 26 1 26 26 1 26 26 26 26 26 26 26 26 26 26	p < 0.01 0.01 Exper Mean 182.310 277.600 217.000 327.900 441.400 2141.400 2141.400 2141.400 2141.400 761.200 p < 0.01 trating c 105.000 68.100 148.800 p = 0.18 302.000 415.400 234.600 342.100	SD To 293.9300 364.6000 37.0000 31.1000 922.8500 338.0000 240.2400 1332.8000 240.2400 1332.8000 240.2400 1332.8000 257.3700 100.1100 180.3000	139 139 139 46 16 18 20 30 30 10 25 8 173 89 21 46 156 156 222 10 076	Mean 146.640 178.900 192.000 132.500 424.500 139.590 358.500 16.550 72.800 85.100 237.000 247.600 47.000 239.500	425.0000 482.000	-5 0 5 Standardised Mean Difference	1.493 10 SMD 0.122 0.122 0.122 0.122 0.122 0.122 0.122 0.122 0.122 0.122 0.122 0.122 0.122 0.122 0.122 0.512	95%-Cl 95%-Cl 1.134: 1.852] 95%-Cl 1.[-0.092; 0.339] 1.[-0.092; 0.339] 3.[-0.092; 0.339] 1.[-0.105; 0.646] 2.[-0.219; 1.243] 1.[-0.105; 0.646] 2.[-0.219; 1.243] 3.[-0.48], 9.362] 3.[-0.48], 9.362] 3.[-0.48], 9.362] 3.[-0.48], 0.533] 3.[-0.48], 0.533] 2.[-0.189; 0.836] 3.[-0.538; 0.446] 3.[-0.538; 0.446] 3.[-0.538; 0.446] 3.[-0.76; 0.817] 3.[-0.176; 0.530] 4.[-0.176; 0.530] 5.[-0.24], 0.529] 5.[-0.24], 0.529] 5.[-0.24], 0.529] 5.[-0.24], 0.529] 5.[-0.26], 0.510] 5.[-0.85], 0.446] 5.[-0.26], 0.549] 5.[-0.26], 0.530] 5.[-0.26], 0.530] 5.[-0.26], 0.549] 5.[-0.26], 0.549] 5.[-0.26], 0.549] 5.[-0.26], 0.549] 5.[-0.26], 0.363] 5.[-0.36], 0.36], 0.363] 5.[-0.36], 0.363] 5.[-0.		Wei (rando 8 8 8 8 8 8 8 8 7 7 4 4 4 4 4 0 6 6 6 6 6 20 20 7 7 5 3 3 8
Fixed effect model Random effects model Heterogeneity: $l^2 = 93\%$, $z^2 = 8$ Residual heterogeneity: $l^2 = 93\%$, $z^2 = 93\%$, $z^2 = 93\%$, $z^2 = 93\%$ Study g = > 10 eosinophils/HP Ho 2018 Fixed effect model Random effects model Heterogeneity: not applicable g = > 70 eosinophils/HP Nakayama 2011 Tojma 2016 Kuuzaki 2016 Kuuzaki 2016 Kuuzaki 2016 Kuuzaki 2017 Uraguchi 2018 Okuda 2018 Vun 2020 Fixed effect model Random effects model Heterogeneity: $l^2 = 87\%$, $z^2 = 2$ g = >10% eosinophils/to Hu 2012 Zhv 2020 Fixed effect model Random effects model Random effects model Heterogeneity: $l^2 = 42\%$, $z^2 = 2$ g = JESREC score Sakuma 2011 Kambara 2017 Hwang 2019 Tauzaki 2019 Tauzaki 2019 Tauzaki 2019 Tauzaki 2019	1348 = 0.6981, 91%, p < Total PF 206 206 1 205 1 205 1 205 1 205 1 205 1 205 1 205 1 206 206 1 207 1 2 2 4 1 2 2 4 1 2 2 4 1 1 2 2 4 1 1 2 2 4 1 1 2 2 4 1 1 5 5 1 6 6 6 6 5 2 2 4 1 1 2 2 4 1 1 2 2 4 1 1 5 5 1 6 6 6 6 5 1 1 2 2 4 1 1 2 2 4 1 1 2 2 4 1 1 2 2 4 1 1 2 2 4 1 1 2 2 3 1 1 2 2 3 1 1 2 2 3 1 1 2 2 3 1 1 2 2 3 1 1 2 2 3 1 1 2 2 3 1 1 2 2 3 1 1 2 2 3 1 1 2 2 3 1 1 2 2 3 1 1 2 1 1 2 1 1 1 1 1 1 1 1 1 1 1 1 1	p < 0.01 0.01 Exper Mean 182.310 277.600 217.000 327.900 441.400 214.000 214.000 214.000 214.000 214.000 761.200 p < 0.01 trating ct 105.000 68.100 148.800 p = 0.18 302.000 415.400 234.600 342.100 891.000	SD To 293.9300 364.6000 37.0000 31.1000 922.8500 338.0000 240.2400 1332.8000 1332.8000 1332.8000 100.1100 180.3000 293.0000 601.1000 153.9000 574.8000	2010 139 139 46 16 16 16 16 16 10 25 8 99 21 173 899 21 156 62 22 10 76 88 88 156 156 156 156 156 156 156 156	Mean 146.640 178.900 192.000 132.500 424.500 139.590 358.500 16.550 72.800 85.100 237.000 247.600 47.000 239.500	425.0000 425.0000 425.0000 425.0000 425.0000 440.0000 440.0000 440.0000 440.0000 440.0000 440.0000 440.0000 440.0000 440.0000 440.0000 440.0000	-5 0 5 Standardised Mean Difference	1.493 10 SMD 0.122 0.042 0.355 0.322 0.325 0.322 0.325 0.322 0.325 0.322 0.325 0.322 0.325 0.322 0.325 0.322 0.325 0.322 0.325 0.322 0.325 0.322 0.325 0.322 0.325 0.322 0.325 0.322 0.325 0.322 0.325 0.322 0.325 0.322 0.325 0.322 0.325 0.325 0.322 0.325 0.177 0.325 0.177 0.195	95%-Cl 95%-Cl 3 [-0.092; 0.339] 3 [-0.092; 0.339] 3 [-0.092; 0.339] 3 [-0.092; 0.339] 4 [-0.105; 0.646] 5 [-0.219; 1.243] 5 [.5.446; 9.366] 5 [-0.219; 1.243] 5 [.5.446; 9.366] 5 [-0.148; 0.738] 8 [-0.144; 1.600] 3 [-0.630; 0.517] 7 [-0.546; 1.260] 9 [-0.176; 0.533] 2 [0.107; 1.357] 2 [0.189; 0.836] 5 [-0.538; 0.446] 0 [-0.176; 0.817] 9 [-0.260; 0.918] 5 [-0.245; 0.545] 9 [-0.260; 0.918] 5 [-0.545; 2.547] 7 [-0.87; 0.440]		Wei (rando 8. 8. 8. 8. 7. 4. 4. 1. 6. 6. 6. 4. 4. 4. 4. 4. 0. 7. 7. 6. 6. 20. 7. 7. 5. 3. 8. 8. 8. 8. 9. 9. 9. 9. 9. 9. 9. 9. 9. 9. 9. 9. 9.
Fixed effect model Random effects mode Heterogeneity: $l^2 = 93\%$, $\tau^2 = 83\%$ Residual heterogeneity: $l^2 = 93\%$ Study g = > 10 cosinophils/HP Ho 2018 Fixed effect model Random effects model Heterogeneity: not applicable g = > 70 cosinophils/HP Nakayama 2011 Tojima 2016 Kouzaki 2016 Kubota 2017 Uraguchi 2018 Okuda 2018 Vuna 2011 Vakayama 2011 Sixed effect model Random effects model Heterogeneity: $l^2 = 87\%$, $\tau^2 = 97\%$ g = >10% cosinophils/tc Hu 2012 Fixed effect model Random effects model Heterogeneity: $l^2 = 42\%$, $\tau^2 = 27\%$ g = JESREC score Sakuma 2011 Kambara 2017 Hwang 2019 Takahashi 2021 Fixed effect model	1348 = 0.6981, 91%, p < Total PF 206 206 1 205 1 205 1 205 1 205 1 205 1 205 1 205 1 206 206 1 207 1 2 2 4 1 2 2 4 1 2 2 4 1 1 2 2 4 1 1 2 2 4 1 1 2 2 4 1 1 5 5 1 6 6 6 6 5 2 2 4 1 1 2 2 4 1 1 2 2 4 1 1 5 5 1 6 6 6 6 5 1 1 2 2 4 1 1 2 2 4 1 1 2 2 4 1 1 2 2 4 1 1 2 2 4 1 1 2 2 3 1 1 2 2 3 1 1 2 2 3 1 1 2 2 3 1 1 2 2 3 1 1 2 2 3 1 1 2 2 3 1 1 2 2 3 1 1 2 2 3 1 1 2 2 3 1 1 2 2 3 1 1 2 1 1 2 1 1 1 1 1 1 1 1 1 1 1 1 1	p < 0.01 0.01 Exper Mean 182.310 277.600 217.000 327.900 441.400 214.000 214.000 214.000 214.000 214.000 761.200 p < 0.01 trating ct 105.000 68.100 148.800 p = 0.18 302.000 415.400 234.600 342.100 891.000	SD To 293.9300 364.6000 37.0000 31.1000 922.8500 338.0000 240.2400 1332.8000 1332.8000 1332.8000 100.1100 180.3000 293.0000 601.1000 153.9000 574.8000	2010 139 139 46 16 16 16 16 16 10 25 8 99 21 173 899 21 156 62 22 10 76 88 88 156 156 156 156 156 156 156 156	Mean 146.640 178.900 192.000 132.500 424.500 139.590 358.500 16.550 72.800 85.100 237.000 247.600 47.000 239.500	425.0000 425.0000 425.0000 425.0000 425.0000 440.0000 440.0000 440.0000 440.0000 440.0000 440.0000 440.0000 440.0000 440.0000 440.0000 440.0000	-5 0 5 Standardised Mean Difference	1.493 10 SMD 0.122 0.042 0.355 0.322 0.325 0.322 0.325 0.322 0.325 0.322 0.325 0.322 0.325 0.322 0.325 0.322 0.325 0.322 0.325 0.322 0.325 0.322 0.325 0.322 0.325 0.322 0.325 0.322 0.325 0.322 0.325 0.322 0.325 0.322 0.325 0.322 0.325 0.325 0.322 0.325 0.177 0.325 0.177 0.195	95%-Cl 95%-Cl 3 [-0.092; 0.339] 3 [-0.092; 0.339] 3 [-0.092; 0.339] 4 [-0.092; 0.339] 5 [-0.092; 0.339] 5 [-0.219; 1.243] 5 [-0.148; 0.738] 5 [-0.176; 0.530] 5 [-0.260; 0.918] 7 [-0.260; 0.918] 5 [-0.263; 0.440] 5 [-0.761; 0.362] 5 [-0.382] 5 [-0.0382] 5 [-0.0382] 5 [-0.382] 5 [-0		Weig (rando 8. 8. 8. 7. 4. 1. 6. 6. 4. 4. 40. 7. 6. 6. 20. 7. 5. 3.8. 6.
Fixed effect model Random effects model Heterogeneity: $l^2 = 93\%$, $z^2 = 8$ Residual heterogeneity: $l^2 = 93\%$, $z^2 = 93\%$, $z^2 = 93\%$, $z^2 = 93\%$ Study g = > 10 eosinophils/HP Ho 2018 Fixed effect model Random effects model Heterogeneity: not applicable g = > 70 eosinophils/HP Nakayama 2011 Tojma 2016 Kuuzaki 2016 Kuuzaki 2016 Kuuzaki 2016 Kuuzaki 2017 Uraguchi 2018 Okuda 2018 Vun 2020 Fixed effect model Random effects model Heterogeneity: $l^2 = 87\%$, $z^2 = 2$ g = >10% eosinophils/to Hu 2012 Zhv 2020 Fixed effect model Random effects model Random effects model Heterogeneity: $l^2 = 42\%$, $z^2 = 2$ g = JESREC score Sakuma 2011 Kambara 2017 Hwang 2019 Tauzaki 2019 Tauzaki 2019 Tauzaki 2019 Tauzaki 2019	1348 = 0.6981, = 0.6981, 91%, p < Total 206 206 1 207 5 6 6 8 14 17 36 12 241 1 = 0.6509, j 0 0 0 1 0 0 1 0 0 1 0 0 1 0 0 1 0 0 1 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0	p < 0.01 0.01 Exper Mean 182.310 277.600 217.000 327.900 441.400 214.000 214.000 214.000 214.000 214.000 761.200 p < 0.01 trating ct 105.000 68.100 148.800 p = 0.18 302.000 415.400 234.600 342.100 891.000	SD To 293.9300 364.6000 37.0000 31.1000 922.8500 338.0000 240.2400 1332.8000 1332.8000 1332.8000 100.1100 180.3000 293.0000 601.1000 153.9000 574.8000	2010 139 139 46 16 16 16 16 16 10 25 8 99 21 173 899 21 156 62 22 10 76 88 88 156 156 156 156 156 156 156 156	Mean 146.640 178.900 192.000 132.500 424.500 139.590 358.500 16.550 72.800 85.100 237.000 247.600 47.000 239.500	425.0000 425.0000 425.0000 425.0000 425.0000 440.0000 440.0000 440.0000 440.0000 440.0000 440.0000 440.0000 440.0000 440.0000 440.0000 440.0000	-5 0 5 Standardised Mean Difference	1.493 10 SMD 0.122 0.122 0.122 0.122 0.122 0.122 0.122 0.122 0.122 0.122 0.122 0.122 0.122 0.122 0.122 0.122 0.122 0.122 0.122 0.512 0.522 0.512 0.512 0.522	95%-Cl 95%-Cl 3 [-0.092; 0.339] 3 [-0.092; 0.339] 3 [-0.092; 0.339] 4 [-0.092; 0.339] 5 [-0.092; 0.339] 5 [-0.219; 1.243] 5 [-0.148; 0.738] 5 [-0.176; 0.530] 5 [-0.260; 0.918] 7 [-0.260; 0.918] 5 [-0.263; 0.440] 5 [-0.761; 0.362] 5 [-0.382] 5 [-0.0382] 5 [-0.0382] 5 [-0.382] 5 [-0	 Weight (fixed) 23.4% 23.4% 2.0% 0.3% 3.6% 5.5% 1.3% 25.4% 3.5% 1.3% 25.4% 1.3% 25.4% 3.5% 1.3% 1.3% 25.4% 3.1% 1.5% 3.1% 3.1% 3.1% 15.6% 3.4% 3.4% 3.4% 2.0% 3.4% 2.0% 4.5% 2.0% 2.0% 2.0% 2.0% 2.0% 2.0% 2.0% 2.0	Wei

Fig. 2. (Continued) (B) Eosinophil count and (C) total immunoglobulin E in eosinophilic and non-eosinophilic chronic rhinosinusitis. SD, standard deviation; SMD, standardized mean difference; CI, confidence interval; HPF, high-power field.

A	Study	Total		rimental SD	Total	Mean	Control SD	Standardised Mean Difference	SMD	95%-Cl	Weight (fixed)	Weight (random)
	g = > 10 eosinophils/HF Snidvongs 2012 Wang 2019 Fadda 2020 Kowalik 2021 Wang 2021 Zhong 2021 Fixed effect model Random effects model	23 48 65 68 16	1.920 56.100 46.000 36.100 11.500 34.170		45 28 16		1.0000 15.2000 17.0000 5.4300 3.3350 5.4300		0.915 0.239 0.074 0.459 -0.178 0.291	[-0.627; 0.495] [0.531; 1.299] [-0.142; 0.621] [-0.366; 0.514] [-0.245; 1.162] [-0.667; 0.311] [0.103; 0.479] [-0.102; 0.602]	3.8% 8.1% 8.2% 6.1% 2.4% 5.0% 33.6%	5.4% 6.5% 6.2% 4.5% 5.8%
	Heterogeneity: $l^2 = 70\%$, $\tau^2 = g = > 70$ eosinophils/HF Nakayama 2011 Fixed effect model	PF	, <i>p</i> < 0.01 15.220	5.1200	46 46	14.570	7.1100		0.108 0.108	[-0.267; 0.482] [-0.267; 0.482]	8.5% 8.5%	6.6%
	Random effects model Heterogeneity: not applicable g = >10% eosinophils/to	otal inf				40.500	7 5000			[-0.267; 0.482]		6.6%
	Hu 2012 Cao 2014 Lin 2014 Lin 2014 Liao 2015 Lin 2016 Zhu 2020 Zhu 2020	20 27 32 60	17.500 5.000 15.700 16.000 19.000 15.800 7.000 3.720	6.3000 2.2230 3.9000 3.2000 7.4120 7.7830 2.2230 0.7410	29 28 29 68	18.500 5.000 13.100 13.500 18.500 13.000 5.500 2.440	7.5980 1.8530 3.3000 3.5000 9.4510 8.5240 2.0300 0.7410		0.000 0.711 0.738 0.058 0.340 0.682	[-0.459; 0.178] [-0.570; 0.570] [0.164; 1.257] [0.217; 1.258] [-0.289; 0.405] [-0.143; 0.823] [0.179; 1.185] [1.201; 2.221]	11.7% 3.7% 4.0% 4.4% 9.9% 5.1% 4.7% 4.6%	6.9% 5.3% 5.5% 5.6% 6.8% 5.9% 5.7% 5.7%
	Xu 2020 Feng 2021 Fixed effect model Random effects model Heterogeneity: $I^2 = 81\%$, $t^2 =$ Fixed effect model	413	6.740 17.870	1.3800 10.2400	50 18 403 671	5.840 14.000	1.6800 7.5900		0.423 0.399 0.497	[0.178; 0.983] [-0.259; 1.105] [0.256; 0.543] [0.161; 0.834] [0.229; 0.447]	7.3% 2.6% 57.9% 	6.4% 4.6% 58.5%
	Random effects model Heterogeneity: $l^2 = 76\%$, $\tau^2 =$ Residual heterogeneity: $l^2 = 1$							-2 -1 0 1 2	0.382	[0.156; 0.608]		100.0%
B	Study	Total	Expe Mean	erimental SD	Total	Mean	Control SD	Standardised Mean Difference	SMD	95%-CI	Weight (fixed)	Weight (random)
	g = > 70 eosinophils/HP Kashiwagi 2019 Fixed effect model Random effects model Heterogeneity: not applicable	17 17	4.770	0.1400	18 18	4.880	0.1500		-0.740	[-1.428; -0.052] [-1.428; -0.052] [-1.428; -0.052]	3.1% 3.1% 	8.0% 8.0%
	g = >10% eosinophils/to Hu 2012 Cao 2014 Liu 2019 Zhu 2020 Xiu 2020 Fixed effect model Random effects model Heterogeneity: $l^2 = 94\%$, $t^2 =$	66 20 31 43 49 209	4.000 4.000 8.000 3.840 4.790	1.6670 2.2380 2.9650	89 29 17 39 50 224	2.000 6.000 1.280	3.1500 4.4470 2.9650 1.4820 3.1100		0.530 0.663 1.711 0.655 0.341	[-0.894; -0.244] [-0.050; 1.110] [0.056; 1.271] [1.201; 2.221] [0.250; 1.060] [0.141; 0.540] [-0.227; 1.401]	14.1% 4.4% 4.0% 5.7% 9.1% 37.3%	10.1% 8.7% 8.5% 9.1% 9.7%
	g = JESREC score Hwang 2019 Kim 2019 Tsuzuki 2019 Ahn 2020 Takahashi 2021 Fixed effect model Random effects model Heterogeneity: l^2 = 73%, r^2 =	77 205 85 18 396	3.000 4.500 23.700 100.000	1.7000	57 76 143	3.900 18.100	1.7500		0.000 0.358 0.611 1.201 0.415	[-0.718; 0.997] [-0.342; 0.342] [0.093; 0.622] [0.595; 1.808] [0.257; 0.573] [0.109; 0.783]	21.2% 19.7% 4.0%	7.0% 10.0% 10.3% 10.3% 8.5%

0.0966, p Fixed effect model 622 566 0.351 [0.229; 0.473] 100.0% \bigcirc Random effects model 0.416 [0.037; 0.794] --100.0% Heterogeneity: $l^2 = 88\%$, $\tau^2 = 0.3433$, p < 0.01Residual heterogeneity: $l^2 = 90\%$, p < 0.01Г -2 0 -1 1 2

Fig. 3. Forest plot. (A) Nasal symptom scores and (B) olfactory dysfunction in eosinophilic and non-eosinophilic chronic rhinosinusitis.

C	Study	Total	•	erimental SD	Total	Mean	Control SD	Standardised Mean Difference	SMD	95%-CI	Weight (fixed)	Weight (random)
	q = > 10 eosinophils/HF	PF						1 :				
	Snidvongs 2012	23	6.000	2.1000	26	3.800	2.7000		0.888	[0.298; 1.478]	3.1%	4.6%
	Aslan 2017	33	2.800	1.1000	20	1.700	0.9000	{ _	1.052	[0.459; 1.645]	3.0%	4.6%
	Shen 2019	59	2.020	0.9100	41	1.900		1_6		[-0.277; 0.521]	6.7%	5.3%
	Ky 2020	28	2.490	0.9530	55	2.030	0.8530	Té		[0.051; 0.975]	5.0%	5.1%
	Fadda 2020	65	8.600	2.5000	45	6.400	2.3000			[0.504; 1.302]	6.7%	5.3%
	Abbas 2021	32	7.000	2.4100	14	5.143	2.4500	- - (0.754	[0.105; 1.402]	2.5%	4.4%
	Zhong 2021	30	10.130	4.9900	35	9.430	4.3100		0.149	[-0.339; 0.638]	4.5%	5.0%
	Fixed effect model	270			236			İ	0.569	[0.385; 0.753]	31.5%	
	Random effects model								0.599	[0.308; 0.890]		34.4%
	Heterogeneity: $I^2 = 58\%$, $\tau^2 =$	= 0.0880,	p = 0.03									
	g = > 70 eosinophils/HF										7	- 10/
	Nakayama 2011	68	4.000	1.5800	46	3.590	1.4700			[-0.111; 0.641]	7.6%	5.4%
	Okuda 2018	12	5.600	1.2000	10	4.500	2.0000			[-0.209; 1.523]	1.4%	3.7%
	Yoshida 2019	25	4.200	0.3000	45	2.300	0.4000			[4.109; 6.107]	1.1%	3.3%
	Nakayama 2019	42	4.800	1.8000	9	4.100	1.8000	1.3.		[-0.341; 1.107]	2.0%	4.2%
	Fixed effect model	147			110					[0.463; 1.057]		40 50/
	Random effects model								1.566	[-0.227; 3.358]		16.5%
	Heterogeneity: $I^2 = 96\%$, $\tau^2 =$	= 3.1902,	p < 0.01									
	g = >10% eosinophils/to	otal inf	iltrating	cells								
	Hu 2012	66	4.000	1.4820	89	3.500	1.4820		0.336	[0.015; 0.656]	10.4%	5.5%
	Cao 2014	20	3.000	1.4820	29	3.000	1.4820	- 	0.000	[-0.570; 0.570]	3.3%	4.7%
	Lin 2014	27	9.300	3.3000	28	7.300				[0.102; 1.189]	3.6%	4.8%
	Lin 2014	32	9.600	2.5000	29	7.800		 (0.647	[0.130; 1.163]	4.0%	4.9%
	Lin 2016	35	9.200	5.1890	32	7.200	5.1890		0.381	[-0.103; 0.865]	4.6%	5.0%
	Zhu 2020	43	8.000	2.9650	39	8.000	2.9650		0.000	[-0.433; 0.433]	5.7%	5.2%
	Xu 2020	49	3.920	1.2000	50	3.780	1.1700		D.117	[-0.277; 0.512]	6.9%	5.3%
	Yao 2020	12	3.500	2.4090	18	4.000	1.4820	- 	0.256	[-0.990; 0.478]	2.0%	4.1%
	Fixed effect model	284			314					[0.096; 0.421]	40.4%	
	Random effects model							¢.).256	[0.066; 0.446]		39.6%
	Heterogeneity: $I^2 = 23\%$, $\tau^2 =$	= 0.0173,	p = 0.24									
	g = JESREC score											
	Nakayama 2019	20	4.300	2.0000	9	4.100	1.8000		0.100	[-0.687; 0.887]	1.7%	3.9%
	Tsuzuki 2019			11.0000			11.9000			[0.596; 1.142]	14.3%	5.6%
	Fixed effect model	225			85					[0.528; 1.044]	16.0%	
	Random effects model				20			1.6		[-0.155; 1.308]		9.6%
	Heterogeneity: $I^2 = 69\%$, $\tau^2 =$	= 0.2052,	p = 0.07									0.070
	Fixed effect model	926			745					[0.398; 0.605]	100.0%	
	Random effects model								0.581	[0.314; 0.848]		100.0%
	Heterogeneity: $I^2 = 84\%$, $\tau^2 =$											
	Residual heterogeneity: $I^2 = I$	84%, p <	< 0.01					6 -4 -2 0 2 4 6				

Fig. 3. (Continued) (C) Endoscopic nasal polyp scores in eosinophilic and non-eosinophilic chronic rhinosinusitis. SD, standard deviation; SMD, standardized mean difference; CI, confidence interval; HPF, high-power field.

maxillary sinus (-0.077 [95% CI, -0.410 to 0.256], Cochrane Q=17.52, P=0.004, I²=71.5%), ostiomeatal unit (SMD=0.241 [95% CI, -0.068 to 0.551], Cochrane Q=15.52, P=0.008, I²=67.8%), or posterior ethmoid sinus (SMD=0.454 [95% CI, -0.217 to 1.126], Cochrane Q=48.27, P<0.001, I²=91.7%) (Supplementary Fig. 2).

The Egger test and Begg funnel plot analyses for total IgE (P=0.600), nasal symptom scores (P=0.251), olfactory dysfunction (P=0.625), and endoscopic nasal polyp scores (P=0.302) revealed no publication bias in the included studies. However, the Egger test and Begg funnel plot analyses for eosinophil percentage (P=0.0004), eosinophil count (P=0.002), and the wholesinus opacification score on CT (P=0.008) suggested that some source of bias might have been included in this sample of studies. The Duval and Tweedie trim-and-fill method showed there was no significant difference between observed and adjusted values (percentage [1.561, P<0.001 vs. 0.946, P<0.001], count

[1.493, P<0.001 vs. 0.847, P<0.001], whole-sinus opacification on CT [0.824, P<0.001 vs. 0.460, P=0.001]). Therefore, we concluded that the selected studies were not biased and that the results of these studies demonstrated the features associated with ECRS with respect to laboratory, clinical, and radiological findings. The funnel plot analysis results are provided in Supplementary Fig. 3. By contrast, Begg funnel plots and the Egger linear regression test for individual sinus lesions (for example, anterior ethmoid or posterior ethmoid opacification, etc.) were not conducted because of the small number of included studies (<10).

Comparison of comorbidities in ECRS versus non-CRS

Aspirin intolerance (SMD=4.657 [95% CI, 2.793–7.765], P < 0.001, $I^2 = 0.0\%$), allergic rhinitis (SMD=2.008 [95% CI, 1.709–2.360], P < 0.001, $I^2 = 21.0\%$), atopy (SMD=1.643 [1.315–2.053], $I^2 = 38.1\%$), and asthma (SMD=3.562 [95% CI, 3.042–4.170], P < 0.001, $I^2 = 25.5\%$) showed significant associa-

Study	Total	Experi Mean	imental SD	Total	Mean	Control SD	Standardised Mean Difference	SMD	95%-CI	Weight (fixed)	Weight (random)
$g = > 10 eosinophils/HISnidvongs 2012Aslan 2017Wang 2019Shen 2019Ky 2020Fadda 2020Abbas 2021Wang 2021Zhong 2021Fixed effect modelRandom effects modelHeterogeneity: I^2 = 94\%, \pi^2$	23 33 48 59 28 65 32 16 30 334		4.9000 0.9000 4.7500 4.0000 4.8000 4.4500	55 45 14 16	8.800 6.200 8.500 15.710 8.540 13.000 7.786 15.500 19.320	5.5000 3.5000 0.7000 4.6400 4.5000 3.4500 4.0700 5.7900		1.623 3.667 0.072 1.123 0.971 0.932 0.400 -0.204 0.918	[-0.327; 0.470]	1.6% 1.4% 1.6% 3.7% 2.5% 3.6% 1.3% 1.2% 2.4% 19.4%	2.4% 2.3% 2.6% 2.6% 2.6% 2.6% 2.3% 2.2% 2.2% 2.2% 2.2%
g = > 70 eosinophils/HI Nakayama 2011 Tojima 2016 Kouzaki 2016 Baba 2017 Uraguchi 2018 Uraguchi 2018 Okuda 2018 Kashiwagi 2019 Yoshida 2019 Nakayama 2019 Kawasumi 2021 Rha 2021 Fixed effect model Random effects mode Heterogeneity: I ² = 91%, z ²	68 14 17 53 58 12 17 25 42 27 24 374		1.0000 4.7500 4.2500 5.2000 4.8000 3.9000 2.0000 1.3000 4.1000 6.3000	16 18 17 30 30 10 18 45 9 18	13.090 12.600 9.400 13.500 13.500 13.780 13.780 8.600 12.300 7.290 15.000	5.4900 1.3000 5.0000 2.2500 5.8000 3.5000 2.5000 0.8000 5.0000 5.3000 5.3000		- 3.492 1.261 1.263 0.713 0.058 -0.155 1.007 4.328 0.786 1.627 -0.094 0.713	[0.251; 1.174] [-0.383; 0.499] [-0.996; 0.686] [0.298; 1.715]	4.2% 0.4% 1.1% 2.7% 3.0% 0.8% 1.2% 0.7% 1.2% 2.0% 1.2% 2.0%	2.6% 1.6% 2.2% 2.5% 2.6% 2.1% 2.2% 2.6% 2.1% 2.2% 2.3% 2.3% 2.3% 2.3% 2.3%
g = >10% eosinophils/t Hu 2012 Cao 2014 Lin 2014 Lin 2014 Kim 2015 Liao 2015 Meng 2016 Lin 2016 Lin 2016 Lin 2016 Lin 2016 Zhu 2020 Zhu 2020 Zhu 2020 Xu 2020 Yao 2020 Feng 2021 Fixed effect model Random effects mode Heterogeneity: I ² = 73%, x ²	66 20 27 32 36 60 123 35 65 24 43 49 12 16 608	18.500 16.000 17.300 16.000 16.000 18.200 17.200 19.500 12.380 13.000 10.200 19.500 16.560	4.6330 8.1540 4.3000 2.6000 8.8950 7.9680 5.2000 6.6710 5.9300 5.3900 9.6360 2.4100 3.1500	29 28 29 45 68 77 32 21 46 39 50	13.500 17.000 15.000 15.000 15.000 15.700 15.700 17.500 12.020 12.020 12.000 8.220 16.000 8.560	2.0380 6.6710 3.6000 2.8000 9.6360 6.1000 5.9300 4.6330 5.1500 8.1540 3.8800 10.3780 6.5600		-0.135 0.573 0.659 0.122 0.391 0.448 0.344 0.351 0.068 0.111 0.607 0.409 1.242 0.495	[1.108; 1.825] [-0.705; 0.436] [0.033; 1.113] [0.142; 1.176] [-0.316; 0.561] [0.041; 0.742] [-0.140; 0.827] [-0.140; 0.827] [-0.142; 0.562] [-0.323; 0.544] [0.204; 1.010] [-0.330; 1.148] [0.499; 1.985] [0.376; 0.614] [0.238; 0.707]	4.5% 1.8% 2.0% 3.0% 4.8% 7.0% 2.5% 2.4% 3.1% 3.6% 1.1% 1.1% 41.5%	2.6% 2.4% 2.5% 2.6% 2.6% 2.6% 2.5% 2.5% 2.5% 2.6% 2.6% 2.6% 2.2% 34.9%
g = JESREC score Takeno 2013 Hwang 2019 to 2019 Kim 2019 Nakayama 2019 Tsuzuki 2019 Takahashi 2021 Fixed effect model Random effects model Heterogeneity: $I^2 = 83\%, \tau^2$ Fixed effect model Random effects model Heterogeneity: $I^2 = 89\%, \tau^2$ Residual heterogeneity: I^2	11 38 77 20 205 18 402 I = 0.4782, 1718 I = 0.5161,	p < 0.01 p < 0.01	3.1000 5.3000 2.0000 3.3000 5.5000	10 30 57 9	16.000 12.300 10.700	4.2500 4.5000 5.8000 2.0000 5.0000 6.5000 1.6000	4 -2 0 2 4	0.451 0.394 0.000 0.300 0.655 3.061 0.575 0.814 0.635	[0.514; 1.801] [-0.418; 1.321] [-0.90; 0.877] [-0.342; 0.342] [-0.491; 1.092] [2.248; 3.873] [0.402; 0.748] [0.251; 1.377] [0.559; 0.712] [0.588; 1.059]	0.8% 2.5% 5.0% 0.9% 8.1% 0.9% 19.6%	2.3% 2.0% 2.5% 2.6% 2.1% 2.7% 2.1%

Fig. 4. Whole-sinus opacification scores in eosinophilic and non-eosinophilic chronic rhinosinusitis. SD, standard deviation; SMD, standardized mean difference; CI, confidence interval; HPF, high-power field.

tions with ECRS (Fig. 5A-D). Nasal polyp development (SMD=11.203 [4.721–26.587], P<0.001, I²=78.2%) and the occurrence of bilateral nasal polyps (SMD=5.510, [95% CI,

4.311–7.042], P<0.001, I^2 =28.8%) were also significantly associated with ECRS (Fig. 5E and F). A subgroups analysis according to the different diagnostic criteria showed no significant dif-

Study	Experin Events	nental Total	C Events	ontrol Total	Odds Ratio	OR	95%-CI	Weight (fixed)	Weight (random)
g = > 10 eosinophils/HPF Snidvongs 2013 Fadda 2020 Kowalik 2021	4 8 4	41 65 68	002	29 45 28			[0.366; 136.806] [0.756; 239.295] [0.140; 4.711]	3.0% 3.2% 8.5%	3.0% 3.2% 8.5%
Fixed effect model Random effects model Heterogeneity: $I^2 = 40\%$, $\pi^2 = 10\%$	1.0905, p =	174 = 0.19		102		2.319 3.073	[0.608; 8.838] [0.487; 19.386]	14.6% 	14.6%
g = > 70 eosinophils/HPF Tokunaga 2015 Wakayama 2018 Kashiwagi 2019	50 1 3	672 24 17	14 0 0	1044 25 18		5.914 3.255 8.931	[3.243; 10.786] [0.126; 83.898] [0.426; 187.057]	72.4% 2.5% 2.8%	72.4% 2.5% 2.8%
Nakayama 2019 Imoto 2020 Rha 2021	1 3 0	42 48 24	000	9 24 29		0.687 3.769	[0.026; 18.202] [0.187; 75.981]	2.4% 2.9% 0.0%	2.4% 2.9% 0.0%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$. p = 0.78	827		1149	\	5.445 5.445	[3.107; 9.543] [3.107; 9.543]	83.0%	83.0%
g = JESREC score Hwang 2019 Nakayama 2019	0	11 20	0	10 9			[0.054; 39.358]	0.0% 2.4%	0.0%
Fixed effect model Random effects model Heterogeneity: not applicable		31		19			[0.054; 39.358] [0.054; 39.358]	2.4%	2.4%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, Residual heterogeneity: $I^2 = 0\%$, p = 0.53	1032		1270	0.01 0.1 1 10 100	4.657 4.657	[2.793; 7.765] [2.793; 7.765]	100.0% 	100.0%
Study	Experin	nental	C Events	control Total	Odds Ratio	OR	95%-CI	Weight (fixed)	Weigh (random
g = > 10 eosinophils/HPI Wang 2019		48		72			[1.410; 10.369]	2.6%	5.49
Yan 2019 Ky 2020	14	40 28 28	2	16		- 5.250 4.437	[0.998; 27.609]	2.0% 0.9% 2.2%	2.29
Wang 2021 Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$	6), p = 0.77	16 120				1.800 3.698		1.1% 6.9% 	2.59 14.69
g = > 70 eosinophils/HPf Nakayama 2011 Tokunaga 2015	F 43 298	68 672		46 1044	<u> </u>	2.934 1.922		4.3%	8.09
Tojima 2016 Baba 2017	7	14	9	16		0.778		1.3%	2.8
Yoshida 2019 Kawasumi 2021	11	25 27	22			0.821	[0.308; 2.194]	2.7%	5.5
Fixed effect model Random effects model Heterogeneity: $l^2 = 24\%$, $\tau^2 =$		823 = 0.25		1186	\$*	1.869 1.739	[1.551; 2.252] [1.211; 2.497]	74.9%	50.29
g = >10% eosinophils/to Hu 2012	27	66	32			1.233		6.1%	10.39
Liao 2015 Liu 2019 Wang 2019	12 9 38	60 31 68	3	17		1.875		2.8% 1.2% 3.4%	5.6° 2.7° 6.7°
Wang 2019 Lv 2020	45	84	8	30		3.173	[1.270; 7.929]	3.1%	6.2
Zhu 2020 Fixed effect model	4	43 376	2				[0.328; 10.984]	0.8%	1.79
Random effects model Heterogeneity: $I^2 = 26\%$, $\tau^2 =$		= 0.23				2.204	[1.387; 3.505]		35.2
Fixed effect model Random effects model		1319		1681			[1.709; 2.360] [1.637; 2.711]	100.0%	100.0
Heterogeneity: $I^2 = 21\%$, $z^2 = Residual heterogeneity: I^2 = 1$	0.0497, p 1%, p = 0.	= 0.21 33			0.1 0.5 1 2 10				
Study g = > 10 eosinophils/HPF		nental Total	Co Events	ontrol Total	Odds Ratio	OR	95%-CI	Weight (fixed)	Weigh (random
Ho 2018 Kowalik 2021	107 30	206 68	67 9	139 28	-18	1.161 1.667	[0.755; 1.786] [0.660; 4.209]		13.19 6.89
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$,		274		167		1.238 1.238	[0.838; 1.830] [0.838; 1.830]	32.6%	19.99
g = > 70 eosinophils/HPF Kouzaki 2016 Kubota 2017	12 20	17 36	4	18 20		8.400 1.528	[1.829; 38.568] [0.509; 4.586]	2.1% 4.1%	3.49
Kouzaki 2017	13	19 72	5	20 20 58		6.500	[1.603; 26.360] [1.656; 7.452]		3.89
Fixed effect model Random effects model Heterogeneity: $I^2 = 52\%$, $\tau^2 = 0$	0.5080, p =			50		3.513 3.966	[1.302; 12.080]	0.0%	12.7
g = >10% eosinophils/to Hu 2012	26	66	36	89		0.957	[0.499; 1.834]		9.9
Cao 2014 Lin 2014	8 16	20 27	7	29 28		2.095 4.364	[0.610; 7.200] [1.383; 13.772]	3.8%	4.7
Lin 2014 Kim 2015	16 17	32 36	6 11	29 45		3.833 2.766	[1.233; 11.922] [1.076; 7.105]	3.9% 5.6%	5.3
Liao 2015 Lin 2016	15 17	60 35	13 8	68 32		1.410 2.833	[0.608; 3.269] [1.002; 8.009]	7.0% 4.6%	7.79
Liu 2019 Zhu 2020	12 15	31 65	5	17 21		1.516 1.800	[0.426; 5.393] [0.466; 6.954]	3.1% 2.7%	4.59
Yao 2020 Fixed effect model Random effects model Heterogeneity: $l^2 = 11\%$, $\tau^2 = 0$	4 0.0357, p =	12 384 = 0.34	6	18 376		1.000 1.813 1.861	[0.212; 4.709] [1.313; 2.504] [1.313; 2.637]	2.1% 47.7%	3.39 57.09
g = JESREC score	11	44	4	10		33 222	11 533- 740 057	0.5%	1.0
Hwang 2019 Kim 2019 Fixed effect model	11 35	11 77 88	4 24	10 57 67		33.222 1.146 1.347	[1.533; 719.957] [0.574; 2.287] [0.686; 2.644]	0.5% 10.4% 10.9%	1.09
Random effects model Heterogeneity: $l^2 = 77\%$, $z^2 = 6$	4.3749, p =			01			[0.173; 110.069]		10.39
Fixed effect model Random effects model		818		668		1.643 1.902	[1.315; 2.053] [1.394; 2.596]	100.0%	100.09
Heterogeneity: $I^2 = 38\%$, $\tau^2 = 0$ Residual heterogeneity: $I^2 = 32$	0.1443, p = 2%, p = 0.1	= 0.08 12			0.01 0.1 1 10 100				

Fig. 5. Comparison of comorbidities between eosinophilic and non-eosinophilic chronic rhinosinusitis. (A) Aspirin intolerance. (B) Allergic rhinitis. (C) Aatopy. (Continued to the next page)

D	Study	Experin Events		C Events	ontrol Total			•	Odds F	Ratio			OR		95%-CI	Weight (fixed)	Weight (random)
	$\begin{array}{l} g = > 10 \; eosinophils/HI \\ Shidvongs 2013 \\ Sreeparvatathi 2017 \\ Ebenezer 2017 \\ Ho 2018 \\ Xu 2018 \\ Wang 2019 \\ Shen 2019 \\ Ky 2020 \\ Fadda 2020 \\ Abbas 2021 \\ Kowalik 2021 \\ Wang 2021 \\ Zhong 2021 \\ Fixed effect model \\ Random effects model \\ Heterogeneity: I' = 0%, \tau' = 0, \end{array}$	16 8 23 23 107 7 9 8 5 33 4 16 2 8 <i>p</i> = 0.53	41 13 33 37 206 39 48 59 28 65 32 68 16 30 715	531 102 05028 0300	29 13 30 28 139 48 72 41 55 45 14 28 16 35 593					~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	-		3.072 5.333 88.700 2.957 3.814 22.385 3.092 10.084 5.781 4.770 4.579 2.584 5.894 5.894 5.894 2.884 5.894 2.884 5.894 4.111	[1.087; [2.238; [1.235; [0.967; [0.552; [1.041; [1.928; [0.230; [0.683; [0.252;	29.393] 559.717] 8.195] 5.842] 405.596] 9.887] 184.165] 31.893] 11.799] 90.998] 90.998] 9.019] 128.496] 487.790] 5.635]	1.9% 0.9% 2.4% 10.8% 0.3% 0.3% 0.3% 0.3% 0.3% 0.3% 0.3% 0.3	3.1% 1.7% 3.7% 0.8% 0.8% 0.8% 0.8% 0.8% 0.8% 0.8% 0.8
	g = > 70 eosinophils/Hf Nakayama 2011 Tokunaga 2015 Kouzaki 2016 Kubota 2017 Baba 2017 Kouzaki 2017 Okuda 2018 Wakayama 2018 Kashiwagi 2019 Yoshida 2019 Nakayama 2019 Imoto 2020 Kawasumi 2021 Rha 2021 Fixed effect model Random effects model Helerogonsky; $t^{-} = 00\%$, $t^{-} = 0$	18 181 29 49 14 11 17 22 10 45	68 672 17 36 17 19 12 24 17 25 42 48 122 27 24 1060	2 125 0 1 0 0 0 2 0 3 0 1 1 3 0	46 1044 18 20 17 20 25 18 45 9 24 8 18 29 24 1351						-		8.789 2.710 33.105 10.739 5.845 37.095 11.118 6.900 153.288 11.000 13.039 19.462 35.000 5.385 16.841 3.453 9.773	[1.285; [0.251; [1.962; [0.522; [1.306; [7.319; 3 [2.678; [0.712; [2.429; [2.632; [1.261;	3.490] 637.276] 89.717] 128.871] 701.321] 238.755] 38.454] 1210.515] 45.175] 238.920] 155.946] 465.373] 22.987] 318.271]	1.1% 38.9% 0.3% 0.3% 0.3% 0.3% 0.3% 0.3% 0.3% 0.3	2.0% 10.1% 0.8% 1.1% 0.8% 1.7% 0.8% 2.3% 0.8% 0.8% 0.8% 0.8% 0.8% 0.8% 0.8% 0.8
	g = >10% eosinophils/b Hu 2012 Cao 2014 Kim 2015 Liao 2015 Meng 2016 Lia 2016 Xu 2017 Liu 2018 7Wang 2019 7Wang 2019 7Wang 2019 7Wang 2019 Zhu 2020 Lv 2020 Feng 2021 Fixed effect model Random effects model Random effects model	28 25 35 31 17 12 19 23 4 7 0 2	66 20 36 60 123 35 30 31 88 84 65 24 43 12 16 713	cells 32 0 3 2 10 9 9 3 1 2 2 1 4 0 0	89 45 68 772 38 17 40 30 21 46 39 18 18 612								1.158 7.973 2.258 3.000 2.085 7.000 5.087 9.857 4.092 5.202 9.000 1.701 0.379 2.757 3.080	[0.501; [0.560; [1.232; [0.348; [2.364; [1.351; [1.235; [0.892; [1.112; [0.945; [0.457;	175.486 10.168 10.071 5.763 140.995 20.732 23.765 78.660 18.765 24.344 85.708 6.329 143.491] 3.900	5.8% 0.3% 0.9% 4.2% 0.3% 0.3% 0.8% 1.2% 0.8% 1.2% 0.8% 1.0% 0.5% 1.0% 0.5% 0.0% 0.3% 20.7%	6.1% 0.8% 2.0% 5.2% 0.8% 3.4% 2.2% 2.0% 2.0% 2.0% 2.0% 2.0% 3.0%
	g = JESREC score Takeno 2013 Hwang 2019 Kim 2019 Kim 2019 Tauzuki 2019 Fixzed effect model Random effects model Heterogenesity: $\hat{r} = 0, \hat{r}, \hat{r} = 0,$	18 4 13 5 88	33 11 38 77 20 205 384	0 3 3 0 8	16 10 30 57 9 76 198				-				39.387 12.600 2.400 3.656 6.742 6.393 5.399 5.399	[0.586; [0.577; [0.990;	711.051] 270.974] 9.980] 13.504] 138.174] 13.989] 9.576] 9.576]	0.3% 0.3% 1.2% 0.3% 4.1% 7.6%	0.8% 0.8% 2.2% 0.8% 5.1%
	Fixed effect model Random effects model Heterogeneity: $I^2 = 25\%$, $z^2 = 0$ Residual heterogeneity: $I^2 = 24$	1296. p = 1	2872 0.06 7		2754	0.001		0.1	1	10		1000	3.562 4.526	[3.042; [3.570;		100.0% 	100.0%
Ø	Study	Even	rimen ts To	ital otal Eve	Con nts T	trol otal			Odds	s Ratio			OR	,		Weight (fixed)	Weight (random)
	g = > 10 eosinophils/H Ho 2018 Kowalk 2021 Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 =$	1 el	30	206 68 274	67 9	139 28 167			_				1.161 1.667 1.238 1.238	[0.755; [0.660; [0.838; [0.838;	1.786] 4.209] 1.830] 1.830]	26.8% 5.8% 32.6%	13.1% 6.8% 19.9%
	g = > 70 eosinophils/H Kouzaki 2016 Kubota 2017 Kouzaki 2017 Fixed effect model Random effects model Heterogeneity: J ² = 52%, τ ²	el	12 20 13	17 36 19 72	4 9 5	18 20 20 58			_				8.400 1.528 6.500 3.513 3.966	[1.829; [0.509; [1.603; [1.656; [1.302;	4.586] 26.360] 7.452]	2.1% 4.1% 2.5% 8.8%	3.4% 5.5% 3.8%
	$g =>10\% eosinophils/Hu 2012Cao 2014Lin 2014Lin 2014Kim 2015Lin 2016Liu 2019Zhu 2020Fixed effect modelRandom effects modelHeterogeneity: l^2 = 11\%, \tau^2$	el	26 8 16 17 15 17 12 15 4	66 20 27 32 36 60 35 31 65 12 84	36 7 6 11 13 8 5 3 6	89 28 29 45 68 32 17 21 18 376					-		0.957 2.095 4.364 3.833 2.766 1.410 2.833 1.516 1.800 1.813 1.861	[0.499; [0.610; [1.383; [1.233; [1.076; [0.608; [1.002; [0.426; [0.426; [0.4466; [0.212; [1.313; [1.313;	7.200] 13.772] 11.922] 7.105] 3.269] 8.009] 5.393] 6.954] 4.709] 2.504]	11.7% 3.8% 3.8% 5.6% 7.0% 4.6% 3.1% 2.7% 47.7%	9.9% 4.7% 5.2% 6.7% 7.7% 4.5% 4.1% 3.3%
	g = JESREC score Hwang 2019 Kim 2019 Fixed effect model Random effects model Heterogeneity: $I^2 = 77\%$, z^2	el			4 24	10 57 67						_	1.146 1.347 4.360	[1.533; 7 [0.574; [0.686; [0.173; 1	2.287] 2.644] 10.069]	0.5% 10.4% 10.9%	1.0% 9.4% 10.3%
	Fixed effect model Random effects mode Heterogeneity: $I^2 = 38\%$, τ^2 Residual heterogeneity: $I^2 =$	= 0.1443,	p = 0.0	3 18 06		668	0.01	0.1		\$	0 1	ר 00	1.643 1.902	[1.315; [1.394;	2.053] 2.596]	100.0%	100.0%

Fig. 5. (Continued) Comparison of comorbidities between eosinophilic and non-eosinophilic chronic rhinosinusitis. (D) Asthma. (E) Presence of nasal polyp. (Continued to the next page)

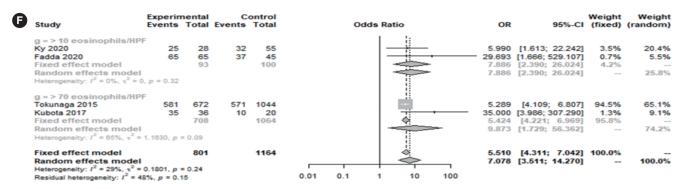


Fig. 5. (Continued) (F) Presence of bilateral nasal polyps. OR, odds ratio; CI, confidence interval.

ferences in comorbidities and nasal polyps (P > 0.05).

Sensitivity analyses

We evaluated differences in pooled estimates by repeating the meta-analysis, each time omitting a different study. All results were consistent with the above results.

DISCUSSION

CRS, which involves inflammation of the nasal mucosa and sinuses, may result from various heterogeneous mechanisms. It thus may give rise to different clinical features in patients and require different treatment methods [3,38]. For example, ECRS is related to several conditions, including allergic rhinitis, asthma, aspirin sensitivity, and atopy [1]. In addition, ECRS has a strong tendency to recur after endoscopic sinus surgery and does not respond well to macrolide treatment, although it responds to systemic steroid treatment [2]. Therefore, accurately defining the CRS endotype can help establish a treatment plan, predict the prognosis, and identify possible comorbidities [62]. At present, histological confirmation is the gold standard for classifying ECRS and non-ECRS [55]. However, a uniform histological standard for diagnosing ECRS has not yet been established [1]. Most studies in this meta-analysis used the histological eosinophil count alone (including the percentage) to classify CRS as eosinophilic or non-eosinophilic. Different cutoff values were applied to define ECRS using tissue eosinophilia, including eight criteria for absolute eosinophil count (≥ 5 , ≥ 8 , ≥ 10 , ≥ 50 , \geq 55, \geq 70, \geq 100, and \geq 120 eosinophils per HPF [×400]), four criteria for the percentage of eosinophils/inflammatory cells $(\geq 10\%, \geq 27\%, \geq 50\%, \text{ and predominant})$, and one criterion based on clinicoradiological findings with the serum eosinophil score (JESREC score \geq 11). However, some cutoff values were used in only one or two studies, and their potential for bias made it difficult to perform a meta-analysis and merge them with other cutoff values. Therefore, we selected cutoff values of \geq 10 and \geq 70 eosinophils per HPF for tissue eosinophilia and $\geq 10\%$ for the percentage of tissue eosinophils for the analysis. We also included the JESREC score, which relies on clinical information, radiological findings, and the serum eosinophil count instead of a histological examination to diagnose ECRS.

In this study, serum eosinophils, IgE levels, nasal symptom scores, and endoscopic nasal polyp scores were significantly higher in ECRS than in non-ECRS. Eosinophils generate several cytotoxic mediators, including eosinophil peroxidase, which is produced under conditions of oxidative stress. These cells can cause serious damage to the epithelium and also play an important role in the pathogenesis of nasal polyps [63]. The amount of free radicals within nasal polyps is also associated with the severity of polyps [64]. Moreover, Th2-mediated inflammation, a major mechanism in ECRS, has also been demonstrated in asthma, allergic rhinitis, nasal polyps, and aspirin sensitivity, which may explain their close association [65-67].

Clinical symptoms may vary in the CRS patient population, and our study shows significant differences in olfaction between ECRS and non-ECRS. These results are similar to those of previous studies [27,30,40] that noted reduced olfaction in patients with ECRS. In this study, patients with ECRS had more bilateral lesions and nasal polyps than patients with non-ECRS. Therefore, we infer that olfaction was affected by the more severe lesions around the ethmoid cells of the olfactory epithelium in ECRS [42].

Significant differences were found in the level of olfactory dysfunction according to the diagnostic criteria used in studies. Two histological criteria (\geq 70% and \geq 10%) did not reveal poorer olfactory function in ECRS than in non-ECRS. One criterion (\geq 70%) was used in only a single study, meaning that the results of this subgroup do not represent the true outcome. All studies using the other criterion (\geq 10%) used a visual analog scale (VAS), whereas most studies using the JESREC criteria used olfactory function tests, such as the butanol threshold test, T&T test, or KVSS II. Since VASs are weakly or moderately correlated with various olfactory function tests, asking patients about olfactory function would at best provide a rough diagnosis of anosmia versus normosmia that would not be reliable [68]. Similarly, in an analysis of the general population of Taiwan, only a weak correlation was found between olfactory function evaluated with various olfactory measurement tools and with a simple self-assessment [69].

Several reports have shown that CT can be useful for diagnosis, in particular in the early stage of ECRS. In ECRS, polyps and mucosal edema often appear around the middle turbinate on CT, which mainly corresponds to the ethmoid sinuses [4,12]. Furthermore, ECRS showed significantly higher rates of opacification of ethmoid and sphenoid sinuses (in particular anterior ethmoid sinuses) on CT than non-ECRS. Since sphenoid sinus lesions cannot be explained by the hypothesis of mucosal edema around the middle turbinate, additional studies are needed to clarify what this finding represents.

Subgroup analyses according to the different diagnostic criteria, including histological findings and clinicoradiological scores, showed significant differences in serum percentages and counts of eosinophils between ECRS and non-ECRS determined using all four diagnostic criteria. The mean peripheral eosinophil count tended to be significantly higher in patients with high mucosal eosinophil counts than in those with low counts. In general, the amount of eosinophils in the blood is representative of the amount of eosinophils in tissue [59]. Therefore, although the criteria had different cutoff values for tissue eosinophils, it is understandable that overall, higher levels of serum eosinophils correspond to ECRS.

To date, histological criteria have been the gold standard for diagnosing ECRS. In our study, several clinical findings, CT findings, and high peripheral eosinophil levels were also confirmed in patients diagnosed with ECRS. Therefore, it may be of clinical benefit to use clinicoradiological findings and/or a peripheral eosinophil scoring system applicable in outpatient clinics where histological testing of tissue eosinophilia is difficult.

This meta-analysis has several limitations. First, the data were collected from a limited number of regions (45 of 55 studies were from East Asia and South Asia), and geographic and genetic factors may influence the clinical characteristics of ECRS. Second, techniques for counting cells per HPF are currently not well standardized. Thus, the results may vary depending on the number of slides used, the level of magnification, the size of the HPF, and the tissue distribution pattern of eosinophils [70]. In addition, since the treatment outcomes were heterogeneous across studies, the diagnostic criteria may have varied accordingly. Therefore, it is possible that the reason for using different diagnostic criteria for ECRS was to more prominently identify outcomes such as specific sinonasal quality of life, recurrence, and the effects of drugs. Third, bias could have been introduced by the medications used prior to clinical manifestations and assessment of eosinophils, because blood and tissue eosinophil counts and nasal polyp size decreased following the initiation of systemic steroid therapy and similar levels were maintained several weeks after the discontinuation of steroids [71-73]. Therefore, clinicians should consider the patient's history of drug treatment when diagnosing ECRS [70]. This may explain some of the heterogeneity in our results. To overcome these limitations and increase the accuracy of the clinical classification of ECRS, it is necessary to standardize technical issues, such as the counting of eosinophils for a conventional ECRS diagnosis, detailed clinical examinations, and meticulous recording of the patient's medication history.

In conclusion, several clinical characteristics, such as higher endoscopic polyp and nasal symptom scores and elevated serum eosinophil counts, are associated with ECRS. Furthermore, sinus opacification (in particular the anterior ethmoid or sphenoid sinuses) on CT is also associated with ECRS. Therefore, if it is difficult to conduct histological examinations to diagnose ECRS, criteria such as the JESREC score could be used.

CONFLICT OF INTEREST

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

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Conceptualization: DHK, SHH. Data curation: SWK, MAB. Formal analysis: SHH, DHK. Funding acquisition: DHK, SWK. Methodology: SWK, MAB; Project administration: DHK, SHH. Visualization: SWK, MAB. Writing–original draft: DHK, SHH. Writing–review & editing: all authors.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found online at https://doi.org/ 10.21053/ceo.2022.00052.

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