Combined European and Japanese criteria to diagnose eosinophilic chronic rhinosinusitis

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Rhinology 63: 5, 0 - 0, 2025

https://doi.org/10.4193/Rhin25.048

Received for publication:

January 22, 2025

Accepted: June 4, 2025

Associate Editor:

Sietze Reitsma

Dear Editor:

The recurrence of nasal polyps has frequently been observed with chronic rhinosinusitis with nasal polyps (CRSwNP), especially with asthma and N-ERD (NSAID-exacerbated respiratory disease) [(1)]. Nasal polyps are often highly infiltrated with eosinophils in the recurrent patients, suggesting the involvement of type 2 inflammation (T2I). Patients with eosinophilic tissue infiltration are diagnosed as having eosinophilic chronic rhinosinusitis (ECRS), a unique CRSwNP subtype. Since the terminology of CRSwNP might include the patients with inflammatory polyps in addition to ECRS, the classification of CRSwNP by endotype is necessary to select the patients who require T2I-targeted biologic treatments. The concept of ECRS was established in 2001 [(2)]. However, a global consensus has not been reached regarding its definition due to the lack of standard histopathologic criteria and methodology for its classification [(3)].

The JESREC study is the largest study to set the criteria for ECRS [(4)]. In the JESREC criteria, bilateral lesions, nasal polyps, and ethmoid sinus involvement are scored as 3, 2, and 2, respectively (Table S1). The percentage of blood eosinophil counts (BEC) in lymphocytes (≤2%, ≤5%, ≤10%, or >10%) is scored as 0, 4, 8, or 10, respectively. The total score of ≤11 together with 70 or more nasal polyp tissue eosinophils/high power field (HPF) is considered as ECRS. In the EPOS2020 criteria, however, only 10 or more nasal polyp tissue eosinophils/HPF with bilateral lesions are required to diagnose ECRS [(5)]. Based on the EPOS2020 criteria, more than 50% of patients with CRS were diagnosed as having ECRS [(6)]. Although T2I may be related to a large proportion of the patients with CRS, not all of them experience recurrence. Therefore, useful criteria with high sensitivity and specificity for the diagnosis of ECRS, which require biologic treatments are necessary.

To establish the criteria of ECRS, we examined the factors associated with recurrence of nasal polyps after surgery. Ninety-eight patients after surgery were included. Factors associated with recurrence were evaluated using multivariate analysis and a machine-learning approach. Patient characteristics and methods are shown in supplementary data. Recurrent nasal polyps were observed in 38% of patients. One-year and 3-year remission rates were 85% and 60%, respectively (Figure S1A). In the multivariate analysis, tissue eosinophils, but not the percentage of BEC or N-ERD, were significantly associated with recurrence, which was also confirmed in the machine-learning analysis (Figure 1A–B, Table S2, and Figure S1B). Tissue eosinophils have moderate accuracy in detecting recurrence (Figure S1C–E). A tissue eosinophil count of 70 or more/HPF, the threshold used in the JESREC criteria and others [(3)], had the highest Youden's index to detect recurrence.

To establish simple and useful criteria by combining the JESREC and EPOS2020 criteria [(4,5)] for diagnosing ECRS, only the bilateral lesions and the number of eosinophils infiltrating nasal polyp were adopted in the combined criteria (CC-ECRS) (Figure 1C). The threshold of eosinophil infiltration was defined as 70 or more. The patients with bilateral lesions and nasal polyp eosinophil infiltration were considered as ECRS. As shown in Figure 1D and Figure S2A–B, the significance of predicting recurrence was superior using CC-ECRS compared with the other methods. Because of the low recurrence rate, the patients with 10–70 eosinophils in nasal polyps were considered to have probable ECRS in which T2I may take place in etiology, but biologic treatments are unnecessary.

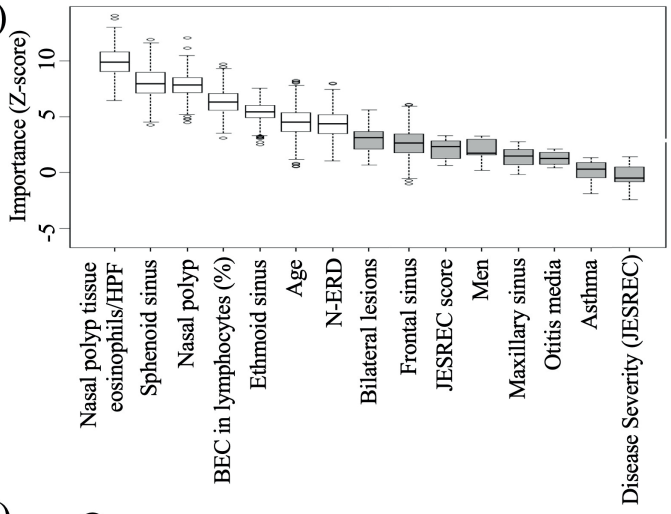
Nasal polyp tissue eosinophils could be an ideal biomarker to detect patients who require biologic treatments. We proposed the CC-ECRS, which integrates the EPOS2020 and JESREC criteria

(A)

	Odds ratio	p value
BEC in lymphocytes (%)	0.97 (0.89 to 1.04)	p=0.49
Nasal polyp tissue eosinophils/HPF	1.02 (1.01-1.03)	**p=0.002**
Asthma or N-ERD	0.97 (0.89-1.04)	p=0.16

BEC: blood eosinophil counts, HPF: high power field, N-ERD: NSAID-exacerbated respiratory disease.

(B)



(C)

Combined diagnostic criteria (CC-ECRS)	
Probable ECRS	**ECRS**
Bilateral primary chronic rhinosinusitis **with**	
Nasal polyp tissue eosinophils/HPF	
≧10, <70	**≧70**

ECRS: eosinophilic chronic rhinosinusitis, HPF: high power field.

(D)

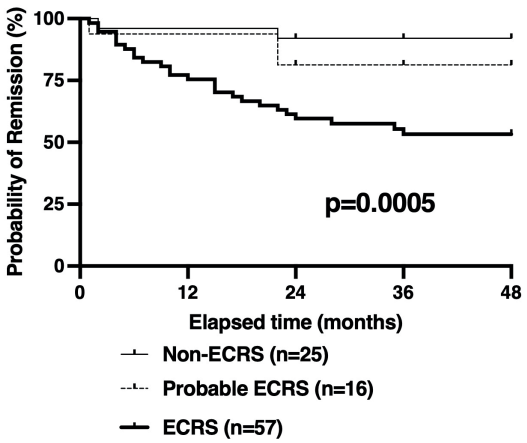


Figure 1. Nasal polyp tissue infiltration of eosinophils and recurrence of CRS. (A) Multivariate analysis to estimate the risk factor of recurrent rhinosinusitis. (B) Machine-learning approach to identify the factors for recurrence. The image depicts a spiral mold, and the factors with white box were significantly associated with recurrence. The detailed methods are available in the supplementary data. (C) Novel diagnostic criteria for eosinophilic chronic rhinosinusitis (CC-ECRS). The patients with bilateral lesions and 70 or more nasal polyp tissue eosinophils/HPF were considered as ECRS. The patients with 10–70 eosinophils in nasal polyps were considered to have probable ECRS. (D) The patients were classified according to CC-ECRS, and the recurrence of rhinosinusitis was calculated using the Kaplan-Meier method (p=0.0005). BEC: blood eosinophil counts, HPF: high power field, N-ERD: NSAID-exacerbated respiratory disease, ECRS: eosinophilic chronic rhinosinusitis.

to diagnose ECRS. Although the utility should be validated in a prospective study, the CC-ECRS criteria would be useful to select patients who require biologic treatments against T2I.

Abbreviations

BEC: Blood eosinophil counts; CC-ECRS: Combined criteria of ECRS; CRS: Chronic rhinosinusitis; CRSwNP: Chronic rhinosinusitis with nasal polyp; ECRS: Eosinophilic chronic rhinosinusitis; N-ERD: NSAID-exacerbated respiratory disease; T2I: Type 2 inflammation

Acknowledgements

The authors also thank Dr. Hajime Kamada (Hokuto Social Medical Corporation) for his excellent suggestions for the manuscript.

Authorship contribution

TK, RS, RH, and RO obtained the clinical data. TK, HY, MK, and RW contributed to write the manuscript. TK, TT, HK, TN, YT, and KK contributed to the statistical analysis. TK and MT designed the study. All the authors reviewed the manuscript.

Conflict of interest

No potential conflicts of interest were disclosed.

Funding

No funds, grants, or other support was received for this manuscript.

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This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

Materials and methods

Patients

We retrospectively analyzed 362 patients who underwent endoscopic sinus surgery in Asahikawa Medical University from 2014 to 2020. Among these patients, tumor, fungal, and odontogenic sinusitis were excluded from the analysis. In the rest of 269 patients, we selected patients who have been followed for at least a year. To avoid the selection bias, all the eligible patients with available biopsy samples were included. Ninety-eight patients fulfilled these criteria and were examined for the further study. Data acquisition and analysis were approved by the Asahikawa Medical University Institutional Review Board (#23014). Informed consent was obtained in the form of opt-out on the website. Corticosteroids were not routinely used in the patients included in this study.

The recorded clinical data were age, sex, nasal fiberscope and computed tomography findings, history of bronchial asthma or NSAID-exacerbated respiratory disease (N-ERD), the percentage of blood eosinophil counts (BEC)/μl in lymphocytes, and nasal polyp tissue eosinophils in x400 high power field (HPF). The presence of nasal polyps was examined at the initial diagnosis in nasoendoscopy. Seventy-nine percents of patients had nasal polyps at the initial diagnosis in nasoendoscopy, whereas nasal polyps were only evident during surgery but not in nasoendoscopy in the rest of patients. Hyposmia was defined by the self-administered odor questionnaire [1], and disease severity was defined according to the JESREC study [2]. The number of nasal polyp tissue eosinophils was calculated as the mean eosinophil counts per four non-overlapping HPF in the nasal polyp from treatment-naïve patients. The remission was defined as no polyps or grade 1 polyps (nasal polyp score: NPS) in nasoendoscopy with no symptoms of anosmia and nasal obstruction, and clinical recurrence was defined as the recurrent or de novo nasal polyp with the NPS of 2.

Machine-learning approach

The analysis of factors related to recurrence was conducted using Boruta [3], a machine-learning approach based on the random forest algorithm [4]. The random forest method constructs numerous decision trees to estimate plausible predictions regarding the relationship between the objective and the explanatory variables. This approach is suitable for multivariate analysis and is a robust non-parametric technique for handling data that do not conform to a normal distribution, which makes it used in clinical research with a low number of samples. Boruta enhances the random forest methodology by incorporating shadow variables, which are randomized versions of original explanatory variable. This allows for the evaluation of the statistical significance of variable importance, thereby strengthening feature selection. Importance metrics for each variable calculated during the construction of the decision trees. The shadow variables, which are expected to have no meaningful relationship with the object variable, undergo significance testing to determine whether the explanatory variables demonstrate statistical significance in comparison to the shadow variables. Explanatory variables that are not statistically significant are excluded from the model, and this iterative process continues until statistically significant variables are identified or a specified number of iterations are completed.

In this study, the "recurrence" data was used as the objective variable, while other parameters were used as explanatory variables. The analysis was performed using the statistical programming language R (Version 4.3.2), with the Boruta package (Version 8.0.0) for R, being carried out. The random forest analysis was performed with the ranger package used in the Boruta function, and the importance metrics were calculated using Z-score. To address missing data (NAs), the impute transadapter function was used. Whether any explanatory variable exceeded the maximum importance score of the shadow variables, termed as a "hit" or "not hit," was determined following a binomial distribution. The significance level for the two-sided test was set at $p = 0.05$. The maximum number of iterations (maxRuns) was set to 2000, and other parameters, such as the number of trees (nTrees), were kept at their default values.

Statistics

Statistical comparison was analyzed using Mann-Whitney U test or Pearson's chi-square test. The predictive value to predict the recurrence was determined using receiver operating characteristic (ROC) analysis. The area under the ROC curve was determined to estimate the recurrence, and Youden's index was calculated as (sensitivity + specificity-1). Recurrence curve was estimated using the Kaplan–Meier method and compared using the log-rank test. Clinical factors were assessed using a univariate log-rank test, and multivariate Cox proportional hazards regression model. Two-sided p value threshold < 0.05 was considered statistically significant. Multiple logistic regression was performed with 3 variables based on the number of recurrent patients. P values were calculated by GraphPad Prism 9.4 (GraphPad Software, Inc, San Diego, CA, USA) and Excel for Mac Ver.16.7 (Microsoft).

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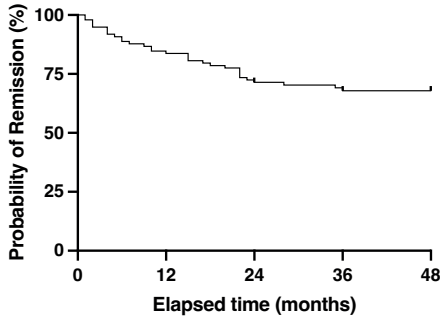
(A)

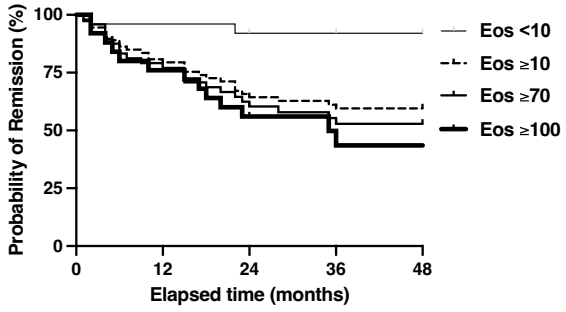


(C)

Nasal polyp tissue eosinophils/HPF	Sensitivity	Specificity	False positive	False negative	Youden's index
≥ 10	95%	38%	62%	5%	131.3
≥ **70**	81%	56%	44%	19%	**135.8**
≥ 100	38%	82%	18%	62%	114.6

HPF: high power field

(B)



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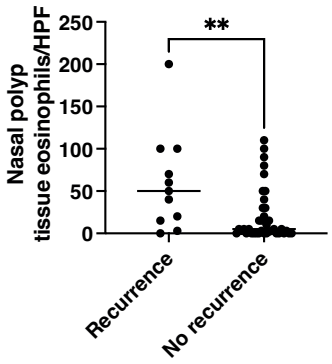

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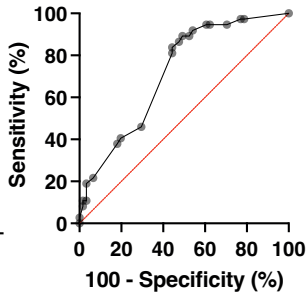

Figure S1. The timing of recurrence and tissue eosinophils in chronic rhinosinusitis. (A) The recurrence of rhinosinusitis was calculated using the Kaplan-Meier method. (B) Sensitivity, specificity, false positive rate, and false negative rate of the number of nasal polyp tissue eosinophils to predict recurrent chronic rhinosinusitis were examined. Each parameter was classified with the number of eosinophils/HPF. (C) The patients were classified according to the number of nasal polyp tissue eosinophils, and the recurrence of rhinosinusitis was calculated using the Kaplan-Meier method (Log-rank test: p=0.001). (D) The number of nasal polyp tissue eosinophils between the patient with recurrent or non-recurrent rhinosinusitis. ***p<0.0001. (E) The area under the receiver operating characteristic (ROC) curve of nasal polyp tissue eosinophils to detect recurrence of rhinosinusitis was 0.72, and 95% confidence interval was 0.61 to 0.82 (p=0.0004). Eos: nasal polyp tissue eosinophils, HPF: high power field.

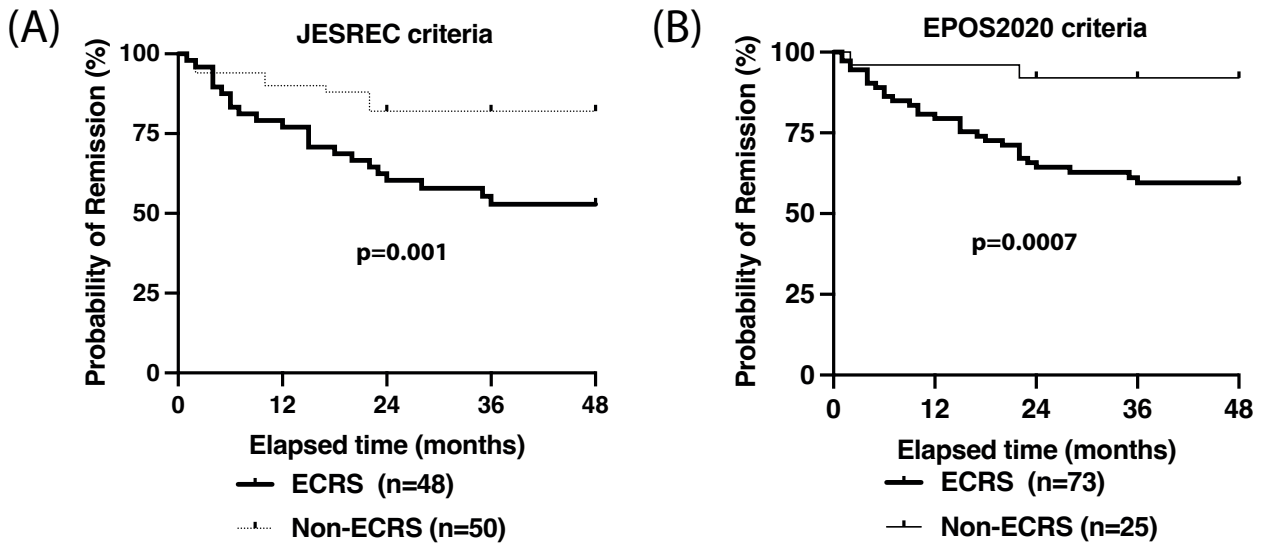

Figure S2. The comparison between JESREC and EPOS2020 criteria to diagnose eosinophilic chronic rhinosinusitis. (A) The patients were classified according to the JESREC criteria, and the recurrence of rhinosinusitis was calculated using the Kaplan-Meier method (Log-rank test: p=0.001). ECRS: eosinophilic chronic rhinosinusitis. (B) The patients were classified according to the EPOS2020 criteria, and the recurrence of rhinosinusitis was calculated using the Kaplan-Meier method (Log-rank test: p=0.0007). ECRS: eosinophilic chronic rhinosinusitis.

JESREC criteria		**EPOS2020 criteria**
Primary chronic rhinosinusitis **with**		Primary chronic rhinosinusitis **with**
JESREC scoring system (Total score: ≥ 11)		
-Bilateral lesions	3	
-Nasal polyp	2	
-Ethmoid ≥ maxillary sinus	2	Bilateral lesions
-BEC in lymphocytes ≤2, ≤5%, ≤10%, >10%	0, 4, 8, 10	
and		**and**
Nasal polyp tissue eosinophils/HPF ≥ **70**		Nasal polyp tissue eosinophils/HPF ≥ **10**

BEC: blood eosinophil counts, HPF: high power field

Table S1. JESREC and EPOS2020 criteria of eosinophilic chronic rhinosinusitis. In the JESREC criteria, the total score of ≤11 with 70 or more nasal polyp tissue eosinophils/HPF is considered as ECRS. In the EPOS2020 criteria, bilateral lesions with 10 or more nasal polyp tissue eosinophil infiltration/HPF are considered as ECRS. ECRS: eosinophilic chronic rhinosinusitis, HPF: high power field.

Population Characteristics		Total N=98	Recurrence N=37	Non-recurrence N=61	p value
Age (years), median (range)		57 (21-83)	50 (24-73)	61 (21-83)	**0.02**
Gender (male/female)		48/50	24/13	24/37	**0.01**
Laterality (bilateral/unilateral)		81/17	35/2	46/15	**0.02**
Sinus involvement	**Maxillary**, N (%)	44 (45)	13 (35)	31 (51)	0.09
	Ethmoid, N (%)	86 (88)	37 (100)	49 (80)	**0.004**
	Frontal, N (%)	60 (61)	28 (76)	32 (52)	**0.02**
	Sphenoid, N (%)	44 (45)	26 (70)	18 (30)	**<0.001**
CRSwNP, N (%)		77 (79)	36 (97)	41 (67)	**<0.001**
Asthma, N (%)		46 (47)	21 (57)	25 (41)	0.12
N-ERD, N (%)		12 (12)	11 (30)	4 (7)	**0.002**
The percentage of BEC in lymphocytes, median (range)		4.5 (0.1-44)	8.2 (0.3-44)	5.3 (0.1-13.6)	**0.001**
JESREC score, median (range)		13 (0-17)	15 (0-17)	11 (0-17)	**0.003**
Nasal polyp tissue eosinophils/HPF, median (range)		40 (0-735)	70 (0-735)	15 (0-200)	**<0.0001**

BEC: blood eosinophil counts, CRSwNP: chronic rhinosinusitis with nasal polyp, HPF: high power filed, N-ERD: NSAID-exacerbated respiratory disease.

Table S2. Characteristics of patients with recurrent chronic rhinosinusitis. The characteristics of the patients with recurrence and non-recurrence were compared.