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Novel scoring system and algorithm for classifying chronic rhinosinusitis: the JESREC Study

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Abstract

Background: Chronic rhinosinusitis (CRS) can be classified into CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). CRSwNP displays more intense eosinophilic infiltration and the presence of Th2 cytokines. Mucosal eosinophilia is associated with more severe symptoms and often requires multiple surgeries because of recurrence; however, even in eosinophilic CRS (ECRS), clinical course is variable. In this study, we wanted to set objective clinical criteria for the diagnosis of refractory CRS.

Methods: This was a retrospective study conducted by 15 institutions participating in the Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis (JESREC). We evaluated patients with CRS treated with endoscopic sinus surgery (ESS), and risk of recurrence was estimated using Cox proportional hazard models. Multiple logistic regression models and receiver operating characteristics curves were constructed to create the diagnostic criterion for ECRS.

Results: We analyzed 1716 patients treated with ESS. To diagnose ECRS, the JESREC scoring system assessed unilateral or bilateral disease, the presence of nasal polyps, blood eosinophilia, and dominant shadow of ethmoid sinuses in computed tomography (CT) scans. The cutoff value of the score was 11 points (sensitivity: 83%, specificity: 66%). Blood eosinophilia (>5%), ethmoid sinus disease detected by CT scan, bronchial asthma, aspirin, and nonsteroidal anti-inflammatory drugs intolerance were associated significantly with recurrence.

Conclusion: We subdivided CRSwNP in non-ECRS, mild, moderate, and severe ECRS according to our algorithm. This classification was significantly correlated with prognosis. It is notable that this algorithm may give useful information to clinicians in the refractoriness of CRS before ESS or biopsy.

Chronic rhinosinusitis (CRS) is one of the most common chronic diseases in Japan and is characterized by nasal purulent discharge, nasal blockage, and hyposmia. In the United States and Europe, CRS is usually classified based on the presence or absence of nasal polyps: chronic rhinosinusitis with nasal polyps (CRSwNP) and chronic rhinosinusitis without nasal polyps (CRSsNP) (1). Several phenotypes of CRS have been reported (2), which produce a complex disease that presents several variants caused by different cellular and molecular mechanisms. CRSwNP is characterized by a Th2-skewed eosinophilic inflammation, while CRSsNP presents a predominant Th1 milieu in Western counties (3). This concept is simple and convenient for clinical studies and practice. However, one type of CRSwNP shows good response to endoscopic sinus surgery (ESS), while the other type of CRSwNP shows a high tendency to recur after ESS and has been classified as refractory CRSwNP.

In Japan and East Asia, neutrophil infiltration has been traditionally dominant in CRSwNP (4–6). However, in recent years, cases of CRSwNP with eosinophilic infiltration have increased in Japan with the westernization of eating habits and environments. Nasal polyps immediately recur after ESS in cases of CRSwNP that present strong eosinophilic infiltration. Because of this, we denominate CRSwNP with eosinophilic infiltration as eosinophilic CRS (ECRS), to differentiate it from CRSwNP with good response to standard therapy (7).

Numerous authors have argued the merit of a clinical classification of CRSwNP according to the degree of eosinophilic infiltration in nasal polyps (8). Mucosal eosinophilic status provides certain prognostic information about disease severity or outcome. CRSwNP patients with mucosal eosinophilia show significantly less improvement in quality of life after ESS. In Western countries, mucosal eosinophilia is defined as >5 or >10 eosinophils per high-power field (HPF) (9, 10), while in Japan mucosal eosinophilia is defined as ≥70, >100, or >120 eosinophils per HPF (5, 11, 12). Thus, diagnosis of eosinophilic infiltration is different among countries and facilities, and there is no consensus.

The present multicenter study investigated what kind of CRS is recurrent or refractory. We paid special attention to the correlation between the level of eosinophilic infiltration and refractoriness of CRS. Furthermore, we created an algorithm to classify CRS prognosis before ESS or biopsy of nasal mucosa.

Abbreviations

AI, aspirin intolerance; AR, allergic rhinitis; AUC, area under the curve; CRS, chronic rhinosinusitis; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; CT, computed tomography; ECRS, eosinophilic chronic rhinosinusitis; ESS, endoscopic sinus surgery; HPF, high-power field; JESREC Study, Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis Study; NSAIDs, nonsteroidal anti-inflammatory drugs; ROC, receiver operating characteristics.

Methods

Study and subjects

This multicenter retrospective study was implemented to examine the factors related to recurrence or refractoriness of CRS in the Japanese population from 2011 to 2012. 'Recurrent' CRS was defined as CRS that presented recurring nasal polyps or sinusitis (nasal symptoms) after ESS. 'Refractory' CRS was defined as recurrent CRS that was not cured by any medical treatment after ESS. This study was conducted in 15 institutions of Japan and related facilities participating in the grants-in-aid program (Ministry of Health, Labour and Welfare Grant; Japan Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis [JESREC] Study). The study was approved by the ethics committee of each institution participating in the JESREC Study.

We assessed patients with CRS (including CRSwNP and CRSsNP) treated with ESS from January 2007 to December 2009 in the 15 institutions. The diagnosis of sinus disease was based on patient history, clinical examination, nasal endoscopy, and computed tomography (CT) of the sinuses, according to the guidelines of the European Position Paper on Rhinosinusitis and Nasal Polyps (1). Our study excluded patients treated with systemic or topical corticosteroids before surgery, patients whose information on systemic or topical corticosteroids was unknown, patients who were followed up for <28 days after surgery, patients whose white blood cell counts were 10 000/μl or more, as well as patients from which there was no pathological specimen.

Preoperative demographic and medical history including sex, age, age of onset, reaction to drugs, history of smoking, complications, and drug allergies were obtained from each patient. Rhinology specialists assessed all participants on seven symptoms and signs before surgery: nasal polyps, viscous rhinorrhea, postnasal drip, facial pain, hyposmia, anosmia, and closure of the olfactory cleft. Blood samples were taken to perform complete blood counts and measure 10 types of antigen-specific IgE. CT findings were graded according to the Lund–MacKay method (13). Recurrence of CRS was defined as the presence of nasal polyps or nasal symptoms in nasal endoscopy.

Histological analysis

Mucosal tissues from patients with CRS were obtained from the nasal polyps or polypoid lesions of the ethmoid cavity

during surgery. Tissue was immediately fixed in 10% formalin, embedded in paraffin, and cut in thin sections. Sections were stained with hematoxylin–eosin. The number of eosinophils in the mucosa was counted at HPF (×400) in the three densest areas with cellular infiltrate beneath the epithelial surface, and the mean number of eosinophils was calculated. Histological examinations were performed by three expert doctors unaware of the clinical data.

Statistical analysis

Relapse-free survival curves of nasal polyps were drawn using the Kaplan–Meier method. Univariate/multivariate Cox proportional hazards models, with the duration of recurrence as the underlying time metric, were prepared to estimate the risk of recurrence of CRS associated with potential predictors, which included clinical variables such as demographic and medical history, symptoms and signs, laboratory data, and CT findings. Hazard ratios with 95% confidence intervals were estimated. Inclusion of variables in the models was based on existing knowledge of risk factors for recurrence of CRS. Factors of the multivariate Cox proportional hazards model included the significant factors identified in univariate models. We applied multiple imputation methods to missing values.

The analysis of the relation between eosinophilic inflammation and refractoriness of CRS was performed using a multiple logistic regression model. There were 17 possible variables with more than 1600 valid values in the model. We followed standard methods to estimate sample size for multiple logistic regression, with at least ten outcomes needed for each independent variable included. With an expected ECRS rate of 40%, we needed 425 patients (170 ECRS patients) to appropriately perform multiple logistic regression with 17 variables. Thus, the sample size of this model was sufficient. First, a linear model was determined, and this was followed by an assessment of the fit of the model and its performance characteristics. We created the diagnostic criterion of ECRS using the significant factors identified with the multiple logistic regression model. To derive cutoff values for the scores of ECRS criterion, we constructed receiver operating characteristics (ROC) curves. Analyses were performed using Stata software v13.0 (StataCorp LP, College Station, TX, USA). $P < 0.05$ was considered statistically significant.

Results

Study population

We enrolled 3241 patients with CRS that underwent ESS in 15 institutions for 3 years. After exclusion of patients according to the abovementioned criteria, 1716 patients (52.9%) were finally assessed. The male/female ratio was 2.2 : 1. Patients were between 18 and 89 years of age (mean 52.4 years). The mean follow-up period was 22.6 months. Three hundred and six (17.8%) of these patients had bronchial asthma, 64 (3.7%) had aspirin intolerance (AI), and 101 (5.9%) had drug allergies. The profiles of the subjects are shown in Table 1.

Factors associated with recurrent chronic rhinosinusitis

We found recurrent CRS or nasal polyps in 396 patients (23.1%). A Kaplan–Meier plot of relapse-free rate related to nasal polyps showed that approximately 20% patients had recurred nasal polyps by the first year, and approximately 10% patients had recurrence by the next year, followed by 5% patients with recurrence every year until 6 years after ESS. Half of the patients had finally recurrent nasal polyps in the sixth year after ESS. No significant difference in recurrence rate of nasal polyps after ESS was observed among the 15 centers (data not shown). The factors significantly associated with recurrence of disease were comorbidity of bronchial asthma, AI, nonsteroidal anti-inflammatory drugs (NSAIDs) intolerance, percentage of eosinophils in peripheral blood, and shadows of sinuses in CT scans. Patients with CRS who presented more than 10% eosinophils in peripheral blood had a significantly higher recurrence of disease than patients who presented 10% or less eosinophils. In relation to shadow of sinuses in CT scans, shadows of ethmoid cells were critical. Patients with CRS who presented dominant shadow of ethmoid cells had recurrences more frequently than patients whose dominant shadow was maxillary sinus (Table 2, Fig. S1). All symptoms, objective signs, history of smoking, and allergen-specific IgE were not significant factors for recurrent CRS.

Relation between tissue eosinophilic infiltration and recurrence of chronic rhinosinusitis

To investigate the relation between eosinophilic infiltration in tissue and recurrence of CRS, in all cases the number of infiltrated eosinophils in the submucosa of the ethmoid cavity or in nasal polyps was counted under the microscope. As a first step, we performed our analysis dividing the patients in quintiles. The ranges of the numbers of eosinophils in nasal polyps were 0–3.3/HPF for the first quintile, 3.3–19.0/HPF for the second quintile, 19.0–66.2/HPF for the third quintile, 66.2–211.9/HPF for the forth quintile, and more than 211.9/HPF for the fifth quintile. Kaplan–Meier plot showed that the forth to fifth quintiles had a significantly higher risk of recurrence of CRS than the first to third quintiles (Fig. 1A). Further analysis showed that the cutoff value of 70/HPF presented the most significant difference ($P < 0.001$, Fig. 1B).

Cases that presented number of eosinophils in submucosa of ethmoid cavity or nasal polyps equal or higher than 70/HPF were defined as ECRS. According to this definition, 672 of the 1716 patients (39.2%) had ECRS, and 1044 (60.8%) had non-ECRS (Table 1). In relation to clinical factors, the positive rate of hyposmia ($P < 0.05$), anosmia ($P < 0.001$), and closing of the olfactory cleft ($P < 0.001$) were significantly higher in ECRS than in non-ECRS, suggesting that the nasal septum was obstructed by nasal polyps.

Table 1 Demographic and clinical profile of the patients

	All subjects (n = 1716)	Non-ECRS (n = 1044)	ECRS (n = 672)	P value
Sex				
Male	1155 (67.3%)	675 (64.7%)	488 (72.6%)	0.001**
Female	525 (30.6%)	352 (33.7%)	177 (26.3%)	
Age (years; mean ± SD)	52.4 ± 16.1	52.5 ± 16.9	52.3 ± 14.6	n.s.
Age of onset (years)				
≤20	135 (7.9%)	91 (8.7%)	44 (6.5%)	n.s.
20–40	387 (22.6%)	222 (21.3%)	165 (24.6%)	
≥40	927 (54.0%)	566 (54.2%)	361 (53.7%)	
Disease side				
Both sides	1152 (67.1%)	571 (54.7%)	581 (86.5%)	<0.001***
One side	522 (30.4%)	450 (43.1%)	72 (10.7%)	
Reaction to drugs				
Antibiotics	125 (7.3%)	73 (7.0%)	52 (7.7%)	n.s.
Oral steroids	117 (6.8%)	51 (4.9%)	66 (9.8%)	<0.001***
Topical nasal steroids	51 (3.0%)	15 (1.4%)	36 (5.4%)	<0.001***
Symptoms and signs				
Nasal polyp	1335 (77.8%)	720 (69.0%)	615 (91.5%)	<0.001***
Viscous rhinorrhea	940 (54.8%)	547 (52.4%)	393 (58.5%)	n.s.
Postnasal drip	690 (40.2%)	437 (41.9%)	253 (37.6%)	n.s.
Facial pain	317 (18.5%)	220 (21.1%)	97 (14.4%)	0.002**
Hyposmia	469 (27.3%)	235 (22.5%)	234 (34.8%)	<0.001***
Anosmia	256 (14.9%)	87 (8.3%)	169 (25.1%)	<0.001***
Closure of the olfactory cleft	609 (35.5%)	246 (23.6%)	363 (54.0%)	<0.001***
History of smoking				
Present smoking	283 (16.5%)	189 (18.1%)	94 (14.0%)	0.004**
Past smoking	244 (14.2%)	133 (12.7%)	111 (16.5%)	
Blood sampling				
White blood cells ($10^3/\mu l$) (mean ± SD)	6.12 ± 1.55	6.04 ± 1.61	6.24 ± 1.47	0.012*
Proportion of eosinophils (%) (mean ± SD)	5.16 ± 4.82	3.82 ± 3.74	7.13 ± 5.54	<0.001***
Antigen-specific IgE				
House dust mite	314 (18.3%)	172 (16.5%)	142 (21.1%)	0.028*
Japanese cedar pollen	461 (26.9%)	226 (21.6%)	235 (35.0%)	<0.001***
Ragweed pollen	71 (4.1%)	34 (3.3%)	37 (5.5%)	0.025*
Orchard grass pollen	108 (6.3%)	60 (5.7%)	48 (7.1%)	n.s.
Candida	46 (2.7%)	24 (2.3%)	22 (3.3%)	n.s.
Aspergillus	30 (1.7%)	20 (1.9%)	10 (1.5%)	n.s.
CT shadow				
Ethmoid > maxillary	611 (35.6%)	238 (22.8%)	373 (55.5%)	<0.001***
Ethmoid = maxillary	499 (29.1%)	305 (29.2%)	194 (28.9%)	
Ethmoid < maxillary	535 (31.2%)	448 (42.9%)	87 (12.9%)	
Complications				
Bronchial asthma	306 (17.8%)	125 (12.0%)	181 (26.9%)	<0.001***
Aspirin intolerance	64 (3.7%)	14 (1.3%)	50 (7.4%)	<0.001***
Allergic rhinitis	604 (35.2%)	306 (29.3%)	298 (44.3%)	<0.001***
Atopic dermatitis	27 (1.6%)	16 (1.5%)	11 (1.6%)	n.s.
Food allergy	34 (2.0%)	18 (1.7%)	16 (2.4%)	n.s.
Drug allergies	101 (5.9%)	44 (4.2%)	57 (8.5%)	<0.001***
NSAIDs	21 (1.2%)	4 (0.4%)	17 (2.5%)	<0.001***
Antibiotics	24 (1.4%)	16 (1.5%)	8 (1.2%)	n.s.
Others	62 (3.6%)	27 (2.6%)	35 (5.2%)	0.005**

CT, computed tomography; ECRS, eosinophilic chronic rhinosinusitis; NSAIDs, nonsteroidal anti-inflammatory drugs; n.s, nonsignificant; SD, standard deviation.

*P < 0.05; **P < 0.01; ***P value < 0.001 (χ^2 test).

Table 2 Multivariate Cox proportional hazards model: recurrence of chronic rhinosinusitis

	Hazard ratio	*P* value
Bronchial asthma	1.43 (1.12–1.82)	0.004**
Aspirin intolerance	3.25 (1.60–6.55)	0.001**
NSAIDs intolerance	2.20 (1.04–4.62)	0.039*
Eosinophils of peripheral blood > 10%	1.52 (1.04–2.25)	0.032*
CT shadow: ethmoid ≥ maxillary	2.06 (1.50–2.84)	<0.001***

CT, computed tomography; NSAIDs, nonsteroidal anti-inflammatory drugs.
Values in parentheses are 95% confidence intervals. *P value < 0.05; **P value < 0.01; ***P value < 0.001.

Factors associated with refractory chronic rhinosinusitis

In the final clinical examination, 190 patients (11.1%) could not be cured, suggesting that they were refractory cases. Factors significantly associated with refractoriness of disease were percentage of eosinophils in peripheral blood and shadows of sinuses in CT scans (Table 3). Patients with CRS with higher than 5% eosinophils in peripheral blood were significantly more difficult to cure compared those with 2% or less eosinophils. Patients with CRS whose dominant disease was ethmoid cells as revealed by CT were also significantly refractory cases, compared to maxillary sinus-dominant cases. Symptoms, objective signs, and history of smoking were not significant factors in the refractoriness of CRS as was recurrence of disease.

Diagnostic criterion of eosinophilic chronic rhinosinusitis

To create the criterion for the diagnosis of ECRS before an operation or biopsy, the significant factors were used as the weighted scores (Table 4, Table S1), and the ROC curve was plotted (Fig. S2A). The area under the curve (AUC) was 0.794. In order not to drop out ECRS, the cutoff value was chosen so that sensitivity might become larger than specificity (Fig. S2B).

Diagnostic items for ECRS were bilateral disease sites, nasal polyps, CT findings, and eosinophilia in peripheral blood. Total clinical score (i.e., JESREC score) was calculated according to each individual score in Table 4. Finally, the cutoff value for the JESREC score for ECRS was defined as 11. If the JESREC score was 11 or higher, the case was diagnosed as ECRS. Sensitivity and specificity of this criterion were 83% and 66%, respectively.

Diagnostic algorithm for refractory eosinophilic chronic rhinosinusitis

The diagnostic algorithm for refractory ECRS was created based on all the results (Fig. 2). First, patients were classified into non-ECRS or ECRS according to the JESREC score (Table 4). ECRS group was classified into three subgroups (i.e., mild, moderate, and severe ECRS) according to factors A and B. Factor A was decided by refractory factors (i.e., >5% eosinophils in peripheral blood, and ethmoid-dominant shadow in CT). Factor B was comorbidity (i.e., bronchial asthma, AI, NSAIDs intolerance).

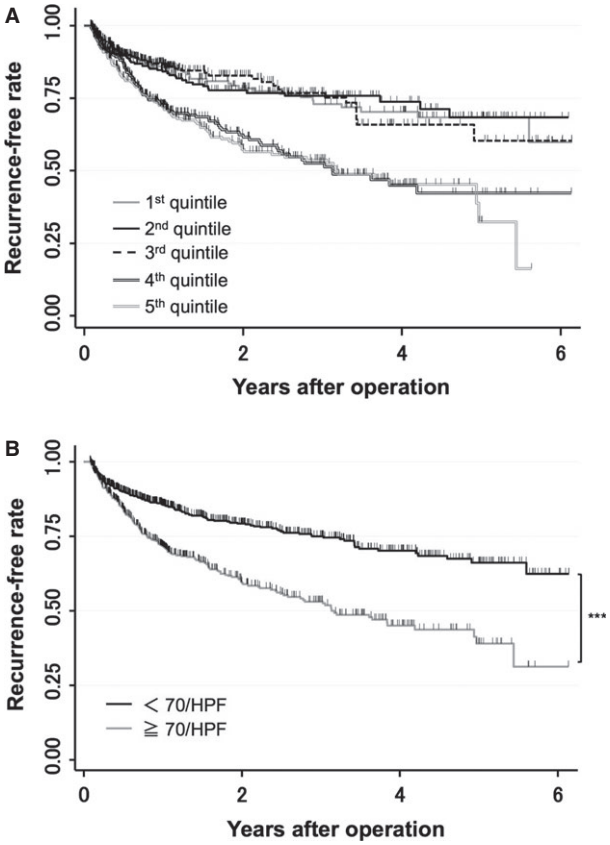

Figure 1 Kaplan–Meier curves of the recurrence-free rate according to the number of eosinophils in nasal polyps. (A) All patients were divided into quintile groups. Eosinophils/high-power field (HPF) in 1st quintile is 0–3.3; 2nd, 3.3–19.0; 3rd, 19.0–66.2; 4th, 6.2–211.9; and 5th, >211.9. (B) When the cutoff value was set to 70/HPF, it was the most significant difference. (***P < 0.001).

When the simulation was performed in the patients who participated in this study, the rates of recurrence were 12.7% for non-ECRS, 23.4% for mild ECRS, 31.1% for moderate ECRS, and 51.8% for severe ECRS. The rates of refractoriness were 3.3% for non-ECRS, 11.7% for mild ECRS, 16.6% for moderate ECRS, and 29.4% for severe ECRS (Fig. 3). There are significant differences among the four groups in both the rate of recurrence (P < 0.001) and refractoriness (P < 0.001). The majority of moderate and severe CRS cases were CRSwNP (546 of 583 cases: 93.7%).

Discussion

In this study, we showed that mucosal eosinophilia of 70 or higher eosinophils/HPF was significantly correlated with recurrence after ESS. A JESREC score consisting of bilateral disease sites, nasal polyps, CT findings, and eosinophilia in peripheral blood was established to make a diagnosis of

Table 3 Multivariate Cox proportional hazards model: refractoriness of chronic rhinosinusitis

	Hazard ratio	*P* value
Peripheral blood eosinophils		
≤2%	1	
2< ≤5%	1.72 (0.95–3.10)	0.072
5< ≤10%	1.86 (1.49–3.32)	0.036*
10% <	2.12 (2.66–4.06)	0.024*
CT shadow: ethmoid ≥ maxillary	2.15 (1.22–3.79)	0.008**

CT, computer tomography. Values in parentheses are 95% confidence intervals. *P value < 0.05; **P value < 0.01.

Table 4 JESREC score criteria for the diagnosis of eosinophilic chronic rhinosinusitis

Factor	Score
Disease side: both sides	3
Nasal polyp	2
CT shadow: ethmoid ≥ maxillary	2
Eosinophils of peripheral blood	
2< ≤5%	4
5< ≤10%	8
10% <	10
Diagnosis	**JESREC score**
ECRS	≥11
Non-ECRS	≤10

CT, computed tomography; ECRS, eosinophilic chronic rhinosinusitis.

ECRS. A JESREC score higher than 11 points was determined as ECRS. Additionally, we classified CRS into four groups according to blood eosinophilia, ethmoid-dominant shadow in CT, and comorbidity (bronchial asthma, AI, NSAIDs intolerance). These four groups were significantly correlated with the rate of recurrence and refractoriness. In our scheme, moderate and severe CRS were considered refractory cases. The most important aspect of our study was to establish a criterion to diagnose and classify ECRS without the use of biopsy or operational specimens.

Mucosal eosinophilic status provides certain prognostic information about severity or outcome of CRSwNP. It is accepted that there is a difference in the pathology of nasal polyps between Western and Asian populations. While approximately 80% of polyps in Western patients are eosinophilic, <50% of polyps in Asian patients show tissue eosinophilia above that seen in control tissues (5–7, 14). However, the interpretation of what is an eosinophilic polyp is different between Western and Asian countries. In this study, the proportion of mucosal eosinophilia defined as higher than 10 eosinophils/HPF was 76.0% (2464 of 3241 cases). This proportion is almost equal to that observed in Western countries (14). The JESREC score and algorithm may also be applicable on other continents as well as Asia. Although we compared the recurrence rate of nasal polyps between patients presenting higher than 10 eosinophils per HPF, and those presenting 10 or less eosinophils per HPF, there was less significant difference in recurrence rate in our patients (data not shown). Neutrophil-dominant infiltrated polyps with 10–70 eosinophils/HPF yielded a large amount of IL-8 in Japanese CRSwNP (12). CRS patients with high levels of IL-8 in nasal lavage are more likely to respond to macrolide treatment (15). Mast cells, tissue plasminogen activator, and factor XIII-A are critical for nasal polyp formation (16–18). Thus, several factors other than eosinophils might contribute to prognosis after ESS in Asian patients with nasal polyps who present 10–70 eosinophils per HPF.

Peripheral blood eosinophilia before operation has also been associated with poor outcome of CRS after ESS (11). More than 6% of eosinophils in peripheral blood was reported to be a predictor for ECRS (19). Eosinophil counts and percentage in peripheral blood significantly correlated with infiltrating eosinophil counts in nasal polyps (20, 21). Thus, peripheral blood eosinophilia might be a biomarker for severe intractable cases.

Mucosal eosinophilia is generally characterized by allergic rhinitis (AR), which is caused by IgE-mediated type I general allergy. Comorbidity of AR was more frequently seen in ECRS (44.3%) compared to non-ECRS (29.3%) (Table 1). A positive rate of serum IgE to Japanese cedar pollen in ECRS was also significantly higher than in non-ECRS (35.0% *vs* 21.6%). However, a positive rate of serum-specific IgE to Japanese cedar pollen is about 55% in the healthy adult Japanese population (22). Thus, AR does not induce nasal tissue eosinophilia in ECRS.

We showed that the predominance of ethmoid sinus inflammation in CT scans was one of the important risk factors of refractory CRS. Several reports suggested that sinus CT scoring was positively correlated with eosinophilic infiltration of nasal mucosa and recurrence of nasal polyps after surgery (9, 23–27). However, the mechanism responsible for the predominance of ethmoid sinus inflammation in refractory CRS remains unclear. One possible explanation is that there are regional differences in molecule expression patterns in the nasal cavity. It has been reported that the inferior turbinate and uncinate process differ dramatically in levels of plasminogen activators and host defense molecules (18, 28, 29). These reports suggested that these regional differences may provide an explanation for the regional specificity of nasal polyp development. Therefore, regional differences between sinuses may account for the predominance of ethmoid inflammation in refractory CRS. Additional studies will be required to determine differences in molecule expression patterns involving sinus inflammation between sinuses. Another possibility is the existence of anatomical differences between each sinus. Namely, in the ethmoid sinus, the volume of cells is small, and the layer of bone forming cells is thin compared to other sinuses. These anatomical differences might confer an increased susceptibility to eosinophilic inflammation in the ethmoid sinus.

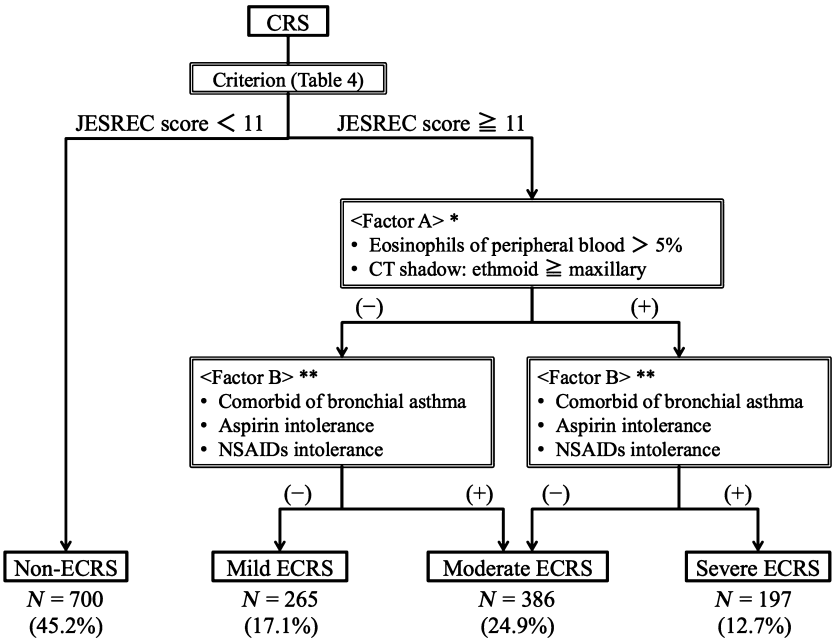

Figure 2 Diagnostic algorithm of refractory even in chronic rhinosinusitis. Factor A is >5% of eosinophils in peripheral blood and ethmoid-dominant shadow in computed tomography, while factor B is comorbid (bronchial asthma, aspirin intolerance, NSAIDs intolerance). *Factor A (+): all of two factors are applied, (−): at least one factor is not applied. **Factor B (+): at least one factor is applied, (−): all of three factors are not applied. Numbers under the figure show the proportion in the participant of this study.

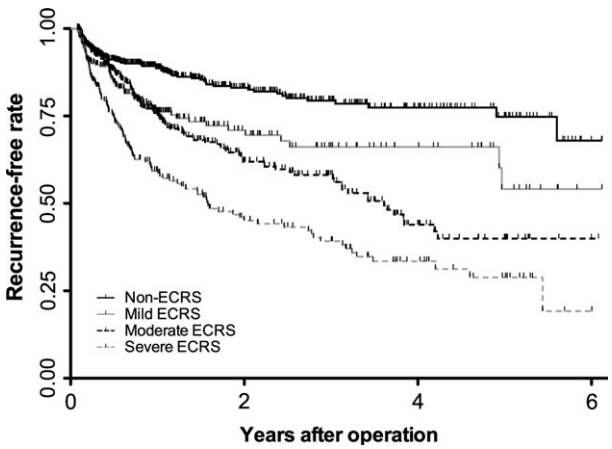

Figure 3 Kaplan–Meier curves of the recurrence-free rate according to the classified groups by the diagnostic algorithm. (Log-rank test: $P < 0.001$).

Bronchial asthma and AI are mainly considered a comorbid condition of CRSwNP, which was confirmed by a large-scale European survey (30). A high percentage of CRSwNP prevalence (90%) was also shown in Japanese AI patients (31). CRS patients with bronchial asthma and AI had a significant increase in peripheral blood eosinophil counts, severer clinical symptoms, and CT scores and required a revision ESS (27).

The major treatment for bronchial asthma has changed from oral corticosteroids to inhaled corticosteroids since 1993 in Japan after the publication of the Asthma Prevention and Management Guideline by the Japanese Society of Allergology (32). This guideline had been accepted by Japanese primary care physicians and internal medicine doctors, including respiratory specialists. As the use of inhaled corticosteroids has increased in Japan, so has ECRS. Inhaled corticosteroids may be noneffective for nasal polyps; thus, oral corticosteroids are now only effective for the treatment of ECRS.

The heterogeneity of CRS may increase the difficulty to diagnose its intractable variant. Although AUC must be 0.9 or more to create a diagnostic criterion with high certainty, its value was actually about 0.8 in this study. To suppress this uncertainty, we created an algorithm. First, ECRS is screened using the JESREC score before operation. Next, ECRS is classified according to the factor of refractoriness and/or recurrence. This algorithm may allow clinicians to decide treatment strategies according to refractoriness before operation. Eventually, it is necessary to confirm the validity of the diagnosis performed before operation by measuring the number of eosinophils in nasal polyps in pathological specimens after surgery. In cases of moderate or severe ECRS, frequent postoperative treatment should be performed, oral or topical corticosteroids should be prescribed, and treatment should be continued for as long as possible. On the contrary, in cases of non-ECRS and mild ECRS, the number of postoperative examinations can be reduced, which can reduce the patient's economical and physical burden.

Our study had some limitations. Some values were missing because of misfiling and the lack of electronic copies of the medical records. We therefore applied multiple imputation

methods to these missing values. The use of this approach results in less biased findings when dealing with missing covariate data. The next step would be a prospective study using the JESREC scoring system and the algorithm.

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Conflicts of interest

All authors state that they have no conflicts of interest to declare.

Author contributions

SF conceived and designed the study. MS, T. Haruna, DA, ST, HI, T. Nakayama, NS, SI, JM, YS, NY, T. Terada, IM, HS, KK, and KY collected clinical data. MO, NO, MY, KH, SH, T. Himi, KI, JI, Y. Iino, RK, HK, MK, TY, T. Miwa, MT, and EN managed the survey of each institution. T. Ninomiya, T. Morikawa, and KT performed histological examinations. T. Tokunaga and T. Ninomiya took part in data management. MU analyzed the data. T. Tokunaga, MS, Y. Imoto, T. Takabayashi, and SF wrote the manuscript. All authors critically read and approved the manuscript.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1 Kaplan-Meier curves of the recurrence-free rate according to (A) comorbid of bronchial asthma, (B) aspirin intolerance, (C) NSAIDs intolerance, (D) the proportion of eosinophils in peripheral blood, and (E) shadow of sinuses in CT scan (MS: maxillary sinus, ES: ethmoid cells). (***$P < 0.001$).

Figure S2 (A) ROC curve for diagnostic criterion of ECRS: AUC was 0.794. (B) Sensitivity-Specificity Plot: In order to screen ECRS, the cutoff value was chosen so that sensitivity might become larger. (Cutoff value of JESREC score was 11, dotted line).

Table S1 Significant factors for eosinophilic chronic rhinosinusitis

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