





## Original Article



# Major basic protein deposited at intra mucosal epithelium with probable eosinophilic chronic rhinosinusitis

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### Conflict of Interest

The authors have no financial conflicts of interest.

## ABSTRACT

**Background:** Eosinophilic chronic rhinosinusitis (ECRS) is diagnosed by Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis (JESREC) scoring system and histopathological eosinophil counts of dissected nasal polyps. Patients with low JESREC score and small number of tissue eosinophils are diagnosed with non-ECRS (NECRS). Due to the 2 parameters of this diagnostic system, chronic rhinosinusitis is to be divided to 4 groups and some patients fall into the 2 groups other than ECRS and NECRS: probable ECRS (pECRS) and probable non-ECRS (pNECRS). We attempted to clarify clinical and histopathological similarities and differences, especially concerning major basic protein (MBP), among those groups.

**Methods:** One hundred twenty-eight patients treated by endoscopic sinus surgery was included. Clinical characteristics were compared among each group, and immunohistological analysis for MBP was performed to 35 randomly selected patients. MBP deposition at intra mucosal epithelium was evaluated by semiquantificational approach.

**Results:** ECRS patients showed significantly higher comorbidity rate with allergic rhinitis (36 patients, 78.3%), asthma (36 patients, 78.3%) compared with other groups. Also, percentage of the patients complaining olfactory dysfunction (42 patients, 91.3%) was significantly higher ( $p < 0.001$ ). Lund-Mackay score (mean, 14.5; 6–24) and recurrence rate (27 patients, 61.4%) was the highest in ECRS patients. Regarding pECRS, the number of patients with olfactory dysfunction (5 patients, 55.6%) was higher than pNECRS and NECRS groups. Also, comorbidity of asthma and percentage of blood eosinophils tended to be higher than those 2 groups. MBP score of pECRS group was significantly higher than NECRS ( $p < 0.05$ ), despite of smaller tissue eosinophil counts.

**Conclusion:** pECRS might share some characteristics with ECRS although tissue eosinophil count was significantly smaller compared with ECRS. The results of this study have shown that MBP score in pECRS nasal polyps was significantly higher than NECRS patients and close to ECRS. That might suggest that eosinophils have existed in the nasal polyps of pPECRS patients at some point before surgery.

**Keywords:** Major basic protein; Eosinophilic chronic rhinosinusitis; JESREC study

**Author Contributions**

Conceptualization: Satoshi Suzuki, Naomi Kudo, Daisuke Matsushita, Ryutaro Hara, Tomoya Miura, Atsushi Matsubara. Formal analysis: Satoshi Suzuki, Naomi Kudo, Daisuke Matsushita, Ryutaro Hara, Tomoya Miura, Atsushi Matsubara. Investigation: Satoshi Suzuki, Naomi Kudo, Daisuke Matsushita, Ryutaro Hara, Tomoya Miura, Atsushi Matsubara. Methodology: Satoshi Suzuki, Naomi Kudo, Daisuke Matsushita, Ryutaro Hara, Tomoya Miura, Atsushi Matsubara. Project administration: Satoshi Suzuki, Naomi Kudo, Daisuke Matsushita, Ryutaro Hara, Tomoya Miura, Atsushi Matsubara. Writing - original draft: Satoshi Suzuki, Naomi Kudo, Daisuke Matsushita, Ryutaro Hara, Tomoya Miura, Atsushi Matsubara. Writing - review & editing: Satoshi Suzuki, Naomi Kudo, Daisuke Matsushita, Ryutaro Hara, Tomoya Miura, Atsushi Matsubara.

**INTRODUCTION**

In Europe and in the United States, chronic rhinosinusitis is generally classified into CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). The former is associated with eosinophil-dominant inflammation whereas the latter with neutrophil-dominant. In Japan, CRSwNP was mainly neutrophil-dominant inflammation as reported by Okuda et al. in 1960s [1]. They could be relatively well-controlled with a combination of endoscopic sinus surgery (ESS) and macrolide therapy (long-term low-dose macrolide administration) in Japan [2, 3]. However, since late 1990s, CRSwNP cases with eosinophil-dominant inflammation began to increase. Nasal polyps recur shortly after ESS despite of postoperative macrolide treatment in those cases. Such intractable type of CRSwNP in Japan was denominated eosinophilic CRS (ECRS) [2, 4].

ECRS is characterized by formation of intractable nasal polyp with a thick basal membrane and significant infiltration of eosinophils, similar to the phenotypes of lower airway remodeling in asthma [3, 5]. Diagnostic criteria have been established from Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis (JESREC) study [6]. Patients are diagnosed with ECRS clinically by JESREC score more than 11 points (Table 1). Definite diagnosis of ECRS was made by histological examination: mean eosinophil count in 3 high power fields must be 70 or more.

Combination of JESREC score and histological examination develop 4 groups including ECRS. When JESREC score is less than 11 and histological eosinophil count is less than 70, the patient is diagnosed with non-ECRS (NECRS). Patients with JESREC score over 11 but with histological eosinophil count less than 70 are regarded as probable ECRS (pECRS) [7]. Conversely, patients with JESREC score less than 11 but with histological eosinophil count over 70 are regarded as probable NECRS (pNECRS). The present study was performed based on the 4 groups and attempted to clarify clinical and histological similarity and differences, especially concerning major basic protein (MBP), among those groups.

**MATERIALS AND METHODS****Patients and tissue preparation**

The present study included a total of 128 patients (85 males and 43 females) aged from 13 to 84 years old, treated by ESS at Hirosaki University Hospital, Otorhinolaryngology Department from April 2016 to December 2020. Patients with 11 or more JESREC score were

**Table 1.** JESREC score for diagnosis of eosinophilic chronic rhinosinusitis

Factor	Score
Disease side: both side	3
Nasal polyp	2
CT shadow: ethmoid $\geq$ maxillary	2
Eosinophils of peripheral blood	
>2%, $\leq$ 5%	4
>5%, $\leq$ 10%	8
>10%	10
Diagnosis	JESREC score
ECRS	$\geq$ 11
NECRS	$\leq$ 10

JESREC, Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis; CT, computed tomography; ECRS, eosinophilic chronic rhinosinusitis; NECRS, non-ECRS.

treated with 10-mg prednisolone and 20-mg esomeprazole for 3 days before surgery. Clinical characteristics such as age of onset, sex, body mass index (BMI), olfactory dysfunction, asthma, allergic rhinitis, laboratory data, Lund-Mackay score (LMS), and respiratory function were obtained from the medical records. LMS is scoring system for severity of chronic rhinosinusitis based on computed tomography findings.

Mucosal tissues were obtained from the nasal polyps or lesions of the ethmoid cavity during ESS, immediately fixed in 10% formaldehyde, and paraffin-embedded tissues. Immunohistological analysis was performed to 35 randomly selected patients: 5 NECRS, 16 pNECRS, 9 pECRS, and 5 ECRS.

This study is approved by ethical committee of Hirosaki University Hospital (approve number: 2022-003).

### Immunohistological analysis

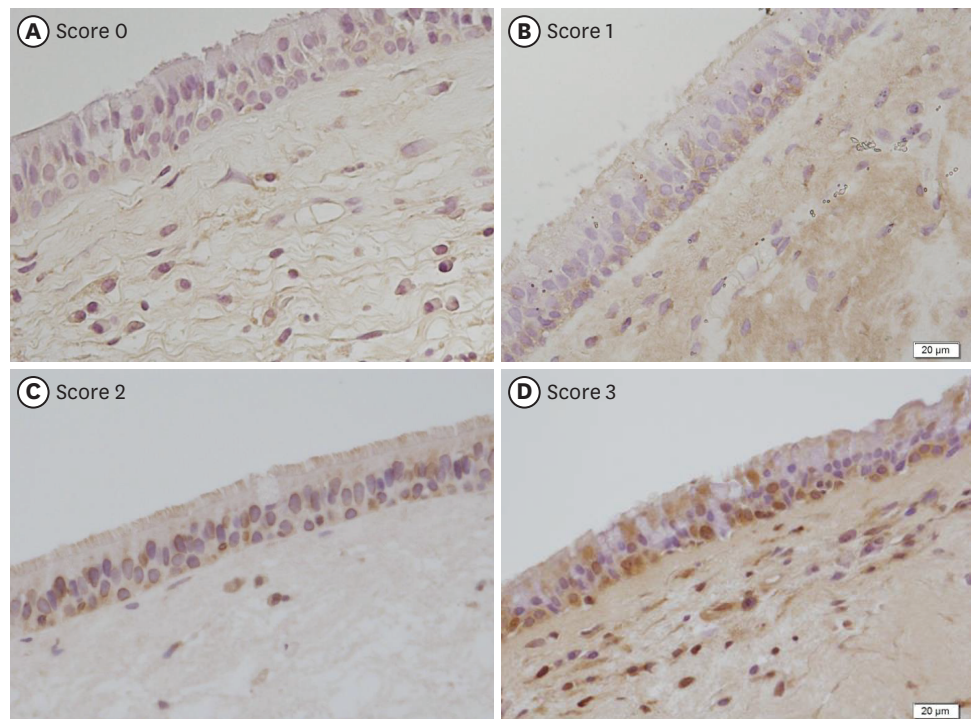
Paraffin-embedded tissues were cut into 4- $\mu$ m sections. Histological eosinophil count was evaluated with hematoxylin-eosin staining sections. Immunohistochemistry was performed as follows: deparaffinized sections were rehydrated through a graded series of ethanol to phosphate-buffered saline. After that, the sections were treated with microwave for antigen activation. Then the sections were incubated in 3% H<sub>2</sub>O<sub>2</sub> for 20 minutes to block endogenous peroxidase activity, followed by Protein Block Serum-Free (Code X0909, Dako, Carpinteria, CA, USA) for 20 minutes. Next, the sections were incubated with anti-Major Basic Protein antibody (1:300, rabbit polyclonal IgG, Abcam, Cambridge, UK) at 4°C overnight. After incubation in the reagents of the secondary antibodies (Dako EnVision+ System- HRP Labelled Polymer Anti-Rabbit) for 40 minutes, the sections were then applied with diaminobenzene/H<sub>2</sub>O<sub>2</sub> for 2 minutes. The sections were counterstained with hematoxylin. Olympus microscope (BX51, Olympus Corp., Tokyo, Japan) and imaging software (DP2-BSW, Olympus Corp.) were used for observation.

### MBP score (Fig. 1)

MBP is one of the cytotoxic proteins contained in eosinophils [8-10], and has been shown to be localized on damaged epithelial surfaces and in mucus plugs in the airways of patients who died from status asthmaticus [11]. MBP deposition at intra mucosal epithelium was evaluated by semiquantificational approach. Specifically, MBP deposition less than one-third of intra mucosal epithelium was regarded as score one (**Fig. 1B**). MBP deposition less than two-third of that was score 2 (**Fig. 1C**), and more than two-third of that was score 3 (**Fig. 1D**). No MBP deposition was score 0 (**Fig. 1A**). The average MBP score of 5 areas for each patient were calculated.

### Statistical analysis

The data of this study were collected, and the result was analyzed by using IBM SPSS Statistics ver. 25.0 (IBM Co., Armonk, NY, USA). A probability value (*p*) less than 0.05 was considered statistically significant.



**Fig. 1.** Major basic protein (MBP) scoring system. (A) Score 0: no MBP deposition. (B) Score 1: MBP deposition less than one-third of intra mucosal epithelium. (C) Score 2: MBP deposition less than two-thirds of mucosa epithelium. (D) Score 3: MBP deposition more than two-thirds of mucosal epithelium.

## RESULTS

### Clinical characteristics (Table 2)

Number of patients complaining olfactory dysfunction was significantly larger in ECRS group than the other groups. Similarly, comorbidity of asthma and allergic rhinitis was significantly higher in ECRS group. LMS was also higher in ECRS group. In contrast, sex and BMI showed no statistically significant difference among the 4 groups. Concerning pECRS patients, the number of patients with olfactory dysfunction was higher than pNECRS and NECRS groups. Also, comorbidity of asthma and percentage of blood eosinophils were higher than pNECRS and NECRS groups.

**Table 2.** Demographic and clinical profile of the patients

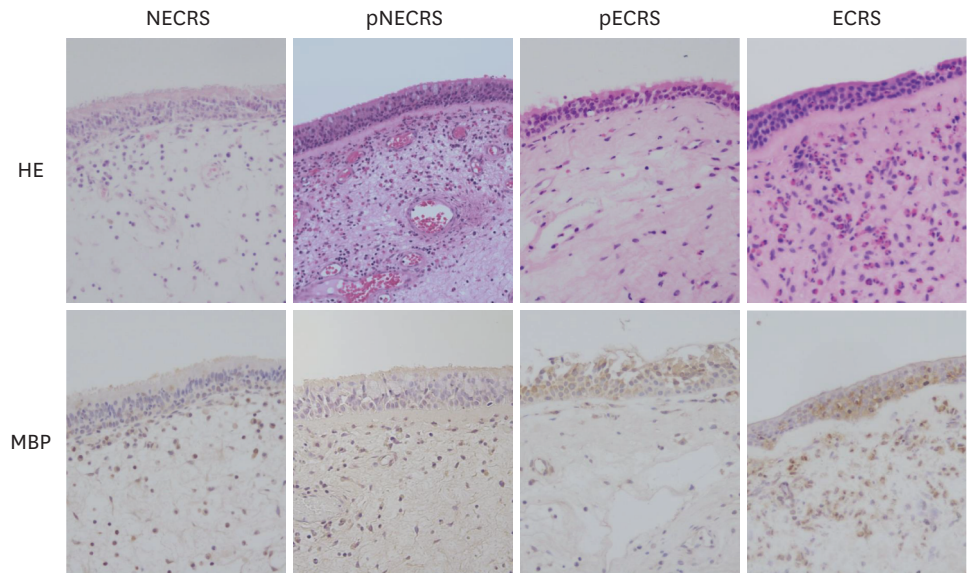
Variable	NECRS (N = 57)	pNECRS (N = 16)	pECRS (N = 9)	ECRS (N = 46)
Age (yr)				
Sex	50	53	54	49
Male	39	14	5	27
Female	18	2	4	19
Body mass index (kg/m <sup>2</sup> )	23.4	24.2	23.8	24.5
Olfactory dysfunction	14 (25.0)	7 (43.8)	5 (55.6)	42 (91.3)
Asthma	1 (1.8)	3 (18.8)	3 (33.3)	36 (78.3)
Allergic rhinitis	22 (39.3)	14 (87.5)	7 (77.8)	36 (78.3)
Blood eosinophil (%)	2.19	2.49	5.92	8.38
Nasal polyp eosinophil (count)	5	154	26.9	148
Lund-Mackay score	7.07	11.9	9.78	14.5
Recurrence	5 (8.8)	3 (20)	0 (0)	27 (61.4)

Values are presented as number (%) unless otherwise indicated.

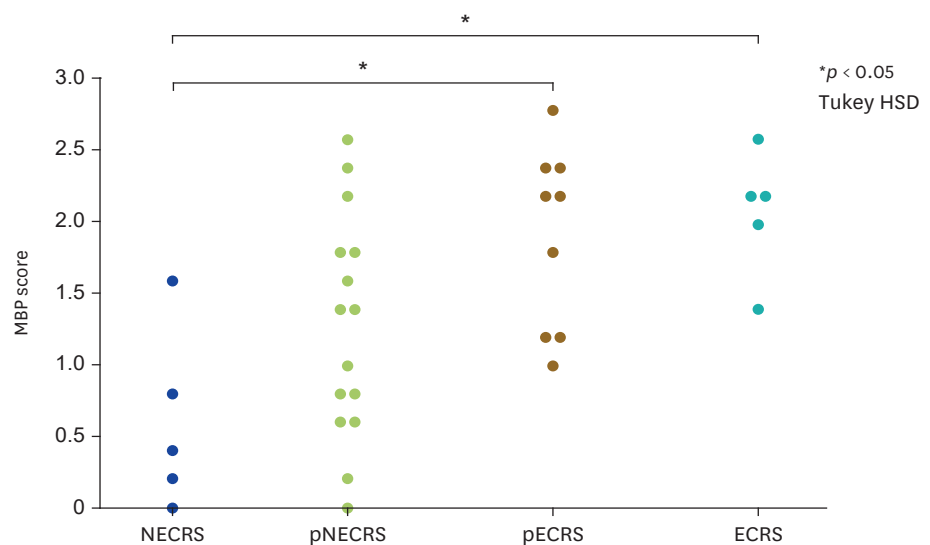
NECRS, non-ECRS; pNECRS, probable non-ECRS; pECRS, probable ECRS; ECRS, eosinophilic chronic rhinosinusitis.

**MBP deposition at intra mucosal epithelium in nasal polyp (Figs. 2,3)**

MBP deposition at intra mucosal epithelium was mainly found in nasal polyp sections of ECRS and pECRS. Especially there are a few eosinophils infiltration at submucosal area NECRS and pNECRS, although we can find more deposition of MBP intra mucosal epithelium with pECRS, but not with NECRS (Fig. 2). The MBP score of each group was shown in Fig. 3. MBP score of ECRS and pECRS group was significantly higher than that of NECRS ( $p < 0.05$ ).



**Fig. 2.** Hematoxylin-Eosin (HE) staining and immunostaining of each group. Although NECRS and pNECRS were found only a few eosinophils infiltrated in the submucosal area, major basic protein (MBP) deposition was found in intra mucosal epithelium of pECRS, but not of NECRS. NECRS, non-ECRS; pNECRS, probable non-ECRS; pECRS, probable ECRS; ECRS, eosinophilic chronic rhinosinusitis. This microscope has a magnification of 200:1.



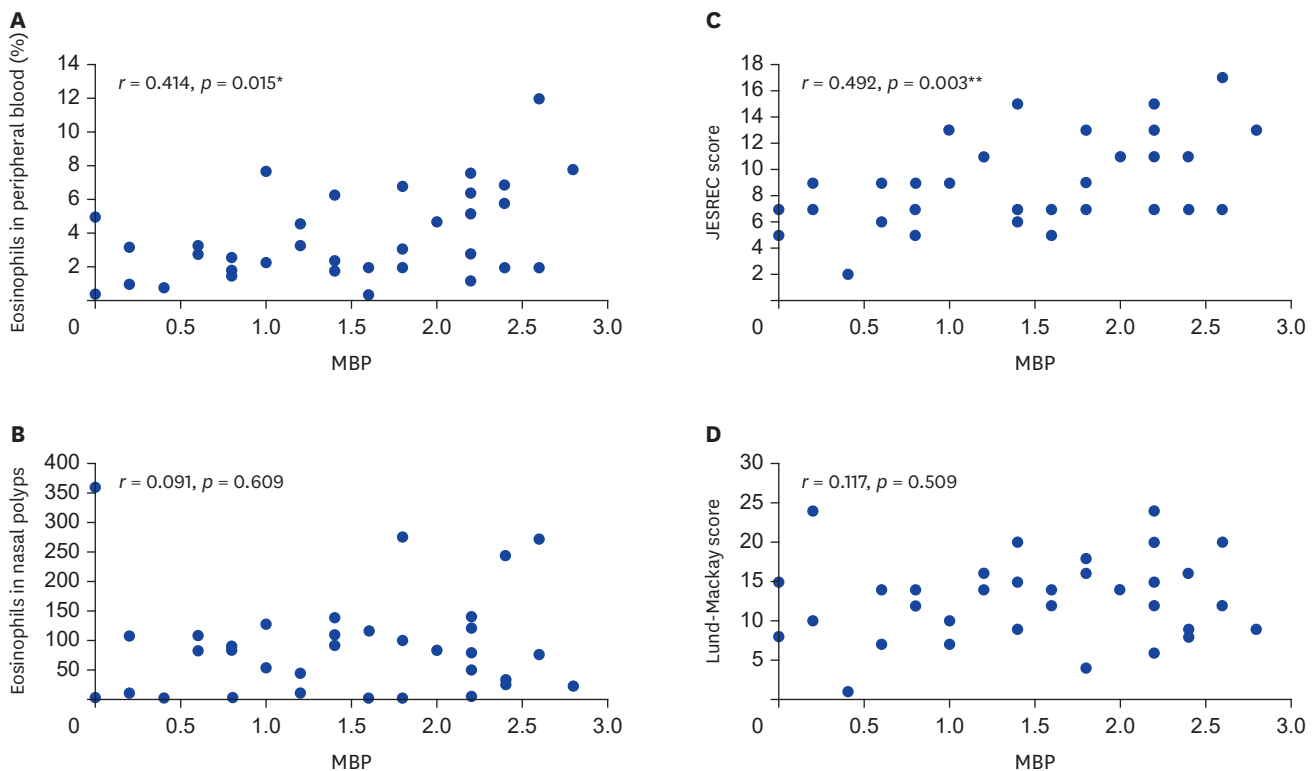
**Fig. 3.** Major basic protein (MBP) score of ECRS and pECRS was significantly higher than that of NECRS ( $p < 0.05$ ). NECRS, non-ECRS; pNECRS, probable non-ECRS; pECRS, probable ECRS; ECRS, eosinophilic chronic rhinosinusitis; HSD, honestly significant difference.

**Correlation of MBP score with clinical findings (Fig. 4)**

Because we found MBP score of ECRS and pECRS was higher than NECRS and pNECRS, it was considered that MBP score correlates with eosinophilic inflammation. Actually, JESREC score, a diagnostic criterion of ECRS, had significant correlation with MBP score ( $r = 0.492$ ,  $p = 0.003$ ) (Fig. 4C). Also, percentage of eosinophils in peripheral blood was significantly higher in the patients with high MBP score ( $r = 0.414$ ,  $p = 0.015$ ) (Fig. 4A). Eosinophil count in nasal polyps or nasal mucosa, counted in high power field in 3 different area, did not have any statistically significant correlation with MBP score ( $r = 0.09$ ,  $p = 0.609$ ) (Fig. 4B). No significant correlation was found between LMS and MBP score either ( $r = 0.117$ ,  $p = 0.509$ ) (Fig. 4D).

**Recurrence rate of each group and correlation with clinical findings (Fig. 5)**

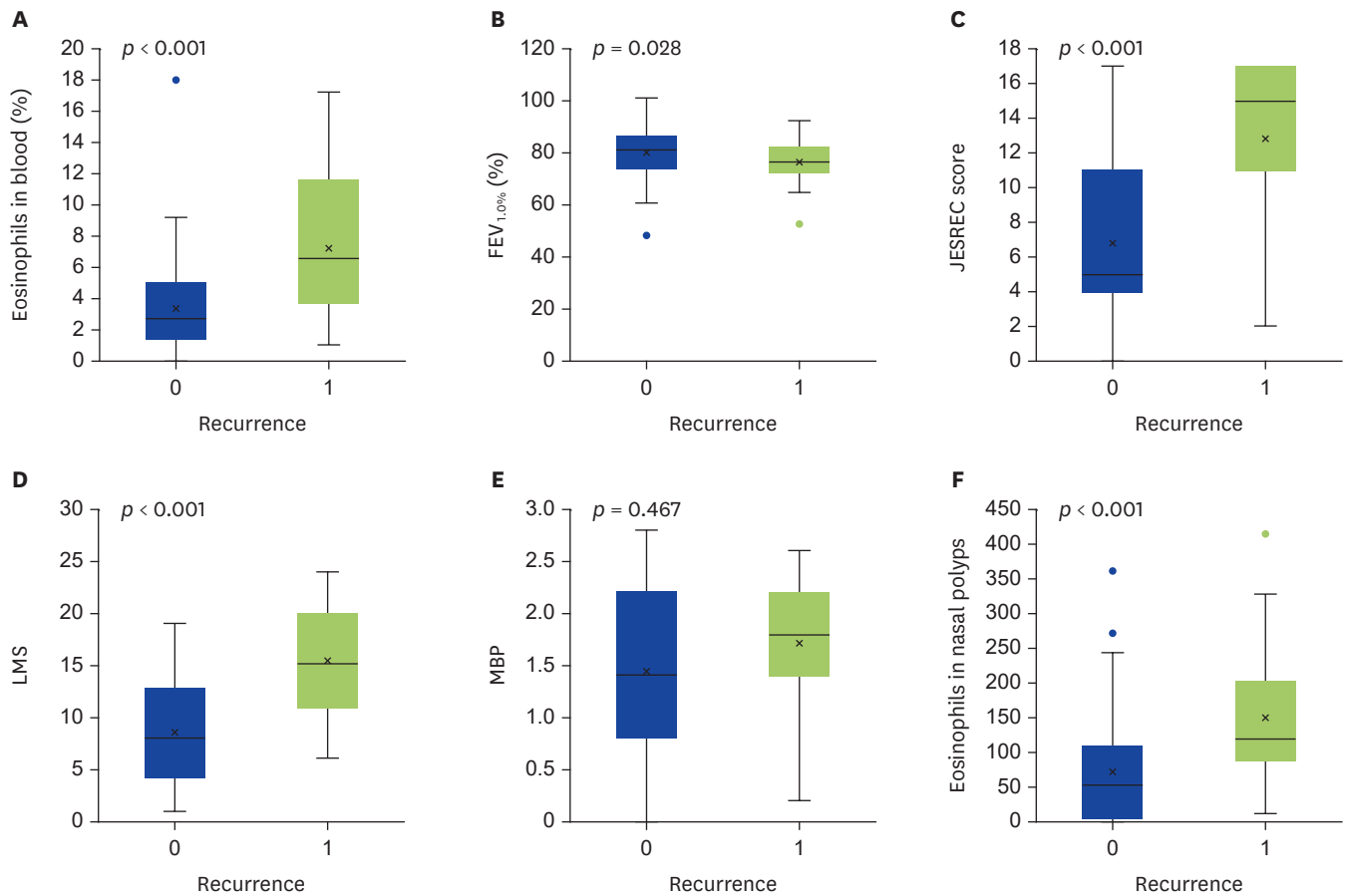
Recurrence of CRS was defined as follows: continuous clinical symptoms; purulent rhinorrhea, postnasal drip, nasal obstruction, and olfactory dysfunction after ESS for more than 28 days. Thirty-five patients (28%) were diagnosed with recurrent CRS. ECRS patients had the highest recurrence rate about 61.4% (Table 2). On the other hand, there was no recurrence with pECRS patients. Investigation of correlation with recurrence rate and clinical findings of 123 patients revealed that peripheral blood eosinophil, JESREC score, LMS, and forced expiratory volume in 1 second significantly correlated with recurrence rate of CRS (Fig. 5). However, recurrence rate had no significant correlation with MBP score of 32 patients; 5 ECRS, 8 pECRS, 15 pNECRS, and 4 NECRS ( $p = 0.467$ ).



**Fig. 4.** Correlation between major basic protein (MBP) score and eosinophil count (A) in nasal polyp (B), JESREC score (C), and Lund-Mackay score (D) eosinophils in the peripheral blood.

JESREC, Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis.

\* $p < 0.05$ . \*\* $p < 0.01$ .



**Fig. 5.** Correlation between recurrence rate and eosinophils in the peripheral blood (A), forced expiratory volume in 1 second (B), JESREC score (C), Lund-Mackay score (LMS) (D), MBP score (E), and eosinophil count in nasal polyp (F). JESREC, Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis; MBP, major basic protein.

## DISCUSSION

ECRS is diagnosed by JESREC score and histological examination of eosinophil counts in the dissected nasal polyps or nasal mucosal tissue. Clinicians occasionally encounter the cases in whom histological eosinophil count does not satisfy the diagnostic criteria of ECRS in spite of high JESREC score. One important objective of the present study is to identify the similarity and difference between such cases and definite ECRS cases.

The results from the analysis of clinical characteristics showed the percentage of patients with olfactory dysfunction, comorbidity of asthma, blood eosinophil were significantly higher in ECRS group than in the other groups. Concerning those 3 characteristics, the percentage of patients was second highest among pECRS patients although the difference was not statistically significant. The results are considered to suggest that pECRS shares something similar with ECRS regarding local condition and systemic background.

Histological deposition of MBP was evaluated by MBP score in this study. It should be noteworthy that MBP score of not only ECRS but also pECRS patients were significantly higher than NECRS patients. It seems contradictory at first sight because histological eosinophil count of pECRS was significantly smaller than ECRS. This result might indicate

that eosinophils existed to no small extent at least some point before surgery. Also, the idea could explain that percentage of the patients with olfactory dysfunction was higher in pECRS patients because MBP would damage olfactory epithelium by its cytotoxic nature. The result that MBP score did not correlate with eosinophil count in nasal polyps (**Fig. 4B**) might suggest the existence of eosinophils in nasal polyps could not be detected after surgery for some reason.

One probable reason for the reduction of histological eosinophil count should be systemic corticosteroid treatment before surgery because it is widely known that corticosteroid induce eosinophil apoptosis and reduce the number of eosinophils [12-14]. Some have reported that preoperative systemic administration of corticosteroid decreased the eosinophil infiltration ratio in nasal polyps [15, 16]. Others have reported that short-term preoperative systemic administration of low-dose corticosteroid did not make a false-negative diagnosis of definite ECRS after surgery [7]. Prednisolone (10 mg/day, for 3 days) and Proton Pump Inhibitor are administered to the patient with JESREC score more than 11 before operation in our department. It is unclear why eosinophils in nasal polyps do not decrease in ECRS patients while histological eosinophil count of pECRS patients do. Although it may involve steroid resistance in some patients, further research is needed with larger sample size.

ECRS had the highest recurrence rate (61.4%: **Table 2**) and recurrence rate of pNECRS was second highest (20%). Notably, there found no recurrence among pECRS patients. In general, the eosinophil level is considered as a marker for severity of eosinophilic inflammation [17, 18]. In the present study, the tissue eosinophil count tended to be greater with an increasing disease severity in CRS patients with or without nasal polyps. Recurrence rate significantly correlated with blood eosinophil count and it seems to suggest relationship between blood eosinophil count and disease severity as reported previously [18]. Similarly, LMS had significant correlation with recurrence rate, which also indicate relationship between recurrence and disease severity [19]. MBP score, in contrast, did not correlate with recurrence rate with no recurrence among pECRS patients. It is difficult to decide whether preoperative treatment and operation were successful for those patients or it merely originated from mild severity of pECRS. However, the good prognosis of pECRS patients in this study might be the result of preoperative systemic steroid and appropriate surgical treatment. In addition, we gave medication of topical nasal corticosteroid spray and leukotriene receptor antagonist to patients with JESREC score over 11 and those treatments could lead to good prognosis.

The limitation of this study is its small sample size and only part of tissue samples could be included for histological analysis. Also, clinical findings such as blood eosinophil and olfactory dysfunction were checked at the first visit to our department while tissue eosinophil count was after systemic corticosteroid administration. Furthermore, we did not check their laboratory data including eosinophils after ESS. Because continuous control of eosinophil inflammation and asthma symptoms are important, condition of pECRS after ESS should be investigated including symptom, number of asthma attack, blood eosinophil, and validity of treatment.

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