Role of serum eosinophil cationic protein in distinct endotypes of chronic rhinosinusitis*

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Abstract

Background: Serum eosinophil cationic protein (ECP) levels affect the surgical outcome of chronic rhinosinusitis (CRS) with nasal polyps. Primary CRS can be classified into type 2 (T2) and non-T2. We aimed to differentiate the role of serum ECP levels in surgical outcomes between the distinct endotypes of primary CRS.

Methods: We prospectively enrolled patients with bilateral primary CRS who underwent surgical treatment with postoperative follow-up for at least 12 months. Endotyping and serum parameter measurements were completed within 1 week before surgery.

Results: In total, 113 patients were enrolled, including 65 with T2 CRS and 48 with non-T2 CRS. Patients in the T2 CRS group with uncontrolled CRS had significantly higher serum ECP levels than those in patients in the non-T2 CRS group. An optimal cut-off value was obtained at 17.0 µg/L using the receiver operating characteristic curve, attaining a sensitivity of 91.7% and specificity of 56.6%. Multivariate logistic regression analysis showed that a higher serum ECP level was an independent factor for postoperative uncontrolled disease. The hazard ratio was 11.3 for the T2 group, with serum ECP levels >17.0 µg/L. In the non-T2 group, no parameters were significantly correlated with postoperative uncontrolled CRS.

Conclusions: Serum ECP levels appear to be a feasible predictor of postoperative uncontrolled disease in patients with T2 CRS as preoperative serum ECP levels >17.0 µg/L in these patients have an approximately 16.7-fold increased risk of postoperative uncontrolled disease and should be closely monitored.

Key words: chronic rhinosinusitis, endotype, serum eosinophil cationic protein, uncontrolled disease, endoscopic sinus surgery

Introduction

Chronic rhinosinusitis (CRS) is a common airway disease that has conventionally been categorized based on phenotypes, including CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) [1-3]. Recently, CRS has progressed from an era focused on phenotype to including endotype-based information [4]. Type 2 (T2)-mediated inflammation is now known to be a predominant component of the pathophysiology in 80–90% of patients with CRSwNP and 30–50% of patients with CRSsNP in Western countries [5,6]. Asian patients with CRS present less T2 inflammation and more mixed inflammation than those in patients of Western countries [7]. In East Asian patients, studies have shown that up to 50% of patients with CRSwNP have non-eosinophilic inflammation, which implies neutrophilic inflammation in response to bacterial infection rather than a purely allergic reaction [8-10]. Patients with CRS that display T2 inflammation as their predominant inflammation type were found to be more prone to therapy resistance and disease recurrence. Recent studies have reported that T2 inflammation causes imbalances between fibrinolytic and coagulative agents, which contributes to the formation of a fibrin mesh, which is suspected to be the primary driver of nasal polyp formation [11].

Eosinophils play a major role in T-helper 2-dominant inflammation. They contain four main granular proteins, including a major basic protein in granule cores surrounded by eosinophil peroxidase, eosinophil-derived neurotoxin, and eosinophil cationic protein (ECP) [12]. Of these matrix granule proteins, ECP

is the best characterized and has been used extensively as a marker for estimating the severity of asthma and other allergic diseases. Serum ECP may activate a continued allergic reaction in the nasal and bronchial epithelium and is clinically valuable in marking eosinophilic inflammation in the respiratory mucosa [13]. ECP is thought to induce the secretion of histamine or leukotrienes and may be correlated with late-phase reactions in patients with asthma [14]. Being a major granule-derived protein, ECP with its cytotoxic activity has been used extensively as a marker for estimating the clinical severity of asthma and other allergic diseases [15]. It may activate a continued allergic reaction in the nasal and bronchial epithelium and is clinically valuable in marking eosinophilic inflammation in the respiratory mucosa [13]. Serum ECP concentration is correlated with the degree of chronic inflammation in the nasal mucosa and may be useful for estimating the progression and determining the prognosis of CRS [16]. Recently, clinical subtypes of CRS and other patient-specific factors have been reported to affect surgical outcomes [17]. Identifying prognostic parameters associated with recurrence in advance is essential for improving surgical quality. In our previous study, we showed that serum ECP could serve as a surgical predictor for patients with CRSwNP, and those with high preoperative serum ECP levels would have an approximately 55-fold increased risk of early postoperative recurrence [18]. As primary CRS has recently tended to be categorized based on endotypes and not only phenotypes, in this study, we aimed to survey the role of preoperative serum ECP level for the surgical outcome in distinct endotypes of primary CRS, attempting to provide a precise preoperative consultation in advance individually.

Materials and methods

Study groups

We prospectively recruited patients diagnosed with bilateral primary CRS refractory after at least 3 months of medical treatment who underwent bilateral functional endoscopic sinus surgery at the Department of Otolaryngology-Head & Neck Surgery, Chang Gung Memorial Hospital. Patients with unilateral sinus diseases, sinonasal neoplasms, fungal rhinosinusitis, previous sinonasal surgery or radiotherapy, age <20 years, and postoperative follow-up duration of <12 months were excluded. All patients with primary CRS met the diagnostic criteria in the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 and endotyping proceeded based on the updated edition accordingly [4,19]. The clinical diagnosis of CRS was made by transnasal endoscopic findings, or computed tomography (CT) scans in the outpatient department. As to the endotyping, patients who had serum blood eosinophil counts ≥250 cells/μL or met at least two of four criteria, serum eosinophil counts ≥150 cells/μL, a positive serum allergy test, total immunoglobulin E (IgE) ≥100 kU/L, and late-onset comorbid asthma, would be classified as the T2 CRS group and others were allocated into the non-T2 CRS group [19]. Demographics, preoperative modified Lund-Kennedy endoscopy (MLK) scores, Lund-Mackay CT (LM) scores, Sino-Nasal Outcome Test-22 (SNOT-22) scores, and laboratory tests were recorded for further analysis. None of the patients received antibiotics, systemic corticosteroids, or biologics within 2 weeks of enrolment. All the patients who participated in this study adhered to the standard treatment for CRS, which involved the regular use of corticosteroid nasal sprays and saline nasal rinses. Asthmatic patients with CRS continued to use steroid inhalers as part of their treatment regimen during the enrollment period. This study was approved by the Institutional Review Board of the Chang Gung Memorial Hospital and informed consent was obtained before enrolment.

Measurements of associated laboratory parameters

Serum ECP and allergy test results (Phadiatop®; ThermoFisher Phadia AB, Uppsala, Sweden) were measured by fluorescent-enzyme immunoassay within 1 week before surgery. The preoperative MLK and LM scores were recorded by two independent surgeons who were blinded to CRS endotyping. The MLK endoscopic scoring system retains the Lund-Kennedy sub-scores of polyps (absent = 0, limited to the middle meatus = 1, extended to the nasal cavity = 2), oedema (absent = 0, mild-moderate = 1, polypoid degeneration = 2), and discharge (absent = 0, hyaline = 1, thick and/or mucopurulent = 2), each receiving a score from 0 to 2, with a higher score indicating a worse outcome(20). The assessment was performed bilaterally, and a combined score (right and left side) of 0–12 was possible. LM scores were evaluated based on opacity and were scored as 0, 1, or 2 for none, partial, or complete opacification over the frontal, anterior and posterior ethmoids, and sphenoid and maxillary sinuses, respectively. The ostiomeatal complex was graded as 0 (no obstruction) or 2 (obstruction present)[21].

Postoperative regimen

After surgery, all patients were scheduled for regular follow-ups at our outpatient department, as previously described(18). Briefly, patients were treated with Augmentin® 30 mg/kg/day for 1 week postoperatively. At 2 weeks after surgery, nasal corticosteroid spray (mometasone furoate, 200 μg/day) and nasal saline irrigation (250 mL once daily) were initiated for 3 months. Postoperative visits were performed weekly for 1 month, monthly for 6 months, and every 3 months for another 6 months. Recurrence of CRS was defined in our previous study as relapse of purulent sinus discharge or recurrence of nasal polyps under endoscopy for at least 2 months despite the rescue regimen of antibiotics, oral steroids, corticosteroid nasal spray, or intensive nasal irrigation during postoperative follow-up [18]. For the concept of patient-centred care, in this study, uncontrolled CRS was defined according to the European Position Paper on Rhinosinusitis and Nasal Polyps guidelines about the CRS disease control in the

Table 1. Demographics of the study groups.

Parameters	T2 group (n=65)	Non-T2 group (n=48)	p-value
Age (years), median (IQR)	41.0 (29.0–53.0)	45.5 (34.0–59.0)	0.281
Gender (male: female)	40: 25	28: 20	0.846
Preoperative MLK score, median (IQR)	6.0 (4.0–9.5)	6.0 (4.0–10.0)	0.929
Postoperative 1-year MLK score, median (IQR)	2.0 (1.0–4.0)	1.0 (1.0–2.0)	0.406
Preoperative LM score, median (IQR)	15.0 (9.0–18.0)	11.0 (8.0–19.8)	0.640
Allergic status, n (%)	45 (69.0%)	6 (12.5%)	< 0.001[a]
Asthma, n (%)	10 (15.0%)	1 (2.0%)	0.023[a]
Current smoking, n (%)	14 (21.5%)	8 (16.6%)	0.632
Uncontrolled CRS, n (%)	12 (18.5%)	5 (10.4%)	0.239
Serum WBC counts (1000/μL), median (IQR)	8.3 (6.1–10.95)	8.9 (7.0–10.7)	0.875
Serum ECP (μg/L), median (IQR)	18.0 (8.4–40.4)	12.2 (6.4–20.4)	0.039[a]
Serum total IgE (kU/L), median (IQR)	191.5 (96.0–442.7)	34.3 (10.7–56.2)	< 0.001[a]
Serum eosinophil counts (/μL), median (IQR)	190.4 (92.6–365.5)	46.4 (10.0–96.3)	< 0.001[a]
Preoperative SNOT-22 score, median (IQR)	51.0 (36.0–67.5)	39.5 (28.3–59.5)	0.044 [a]
Postoperative 1 year SNOT-22 score, median (IQR)	22.0 (13.0–33.0)	22.0 (6.0–36.0)	0.977

[a] Statistically significant. T2, type 2; ECP, eosinophil cationic protein; IgE, immunoglobulin E; IQR, interquartile range; MLK, modified Lund-Kennedy; LM, Lund-Mackay; SNOT-22, Sino-Nasal Outcome Test-22.

2020 edition [4]. The status of CRS disease could be defined as controlled, partially controlled, or uncontrolled, based on objectively determining the degree of subjective symptom reduction, mucosal condition, side effects, need for systemic medications, and need for functional endoscopic sinus surgery. Postoperative MLK and SNOT-22 scores were recorded at 3, 6, and 12 months after surgery.

Statistical analysis

The association between postoperative subjective or objective measurements and medical factors was analysed using Spearman's rank correlation. Intergroup comparisons were performed using Fisher's exact test and Mann–Whitney U test for categorical and continuous variables, respectively. The ideal cut-off value of ECP level to predict postoperative uncontrolled CRS was determined using receiver operating characteristic (ROC) curve analysis, according to Youden's index. By applying the cut-off value of the serum ECP levels, the rates of postoperative uncontrolled CRS until the end of follow-up were compared using Kaplan–Meier curve analysis and log-rank tests, with cases censored at the end of the follow-up. Hazard ratios (HRs) were calculated using the Cox proportional hazards model. Statistical analysis was performed using SPSS 26 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 9.0 (GraphPad Prism Software, Inc., San Diego, CA, USA). The significance level was set at $p < 0.05$. The minimum required sample size was calculated by using the statistical software PASS 2022 (NCSS, LLC, Kaysville, UT, USA) [22], and 46 subjects were required in each study group to have statistic power at 0.9 to detect the difference of serum ECP levels at a two-sided level of 0.05.

Results

Demographics of the study groups

Initially, 170 patients who underwent bilateral endoscopic sinus surgery were enrolled in this study. Eventually, 113 patients who received surgical treatment and completed the postoperative follow-up regimen were enrolled, including 65 in the T2 group and 48 in the non-T2 group. The T2 group comprised 49 patients with CRSwNP and 16 patients with CRSsNP, whereas the non-T2 group included 34 patients with CRSwNP and 14 patients with CRSsNP. The average length of postoperative follow-up was 19.2 months. The clinical characteristics are shown in Table 1. The patients in the T2 CRS group had significantly higher total serum IgE levels, allergic status, serum ECP levels, and serum eosinophil counts than those in patients in the non-T2 CRS group. The differences in subjective disease severity (SNOT-22 scores) between the two groups reached marginal significance ($p = 0.044$), while no other significant differences were found in demographics and objective measurements (MLK and LM scores).

Uncontrolled disease in the T2 CRS group

Among the 65 patients in the T2 group, 12 had postoperative uncontrolled CRS. Among the patients with uncontrolled CRS, there were 3 patients with both purulence and nasal polyps, 5

Table 2. Comparison between the patients without and with postoperative uncontrolled disease in T2 CRS.

Parameters	Without uncontrolled CRS (n=53)	With uncontrolled CRS (n=12)	p-value
Age (years), median (IQR)	41.0 (29.5–51.5)	39.5 (28.0–54.8)	0.819
Gender (male: female)	30: 23	10: 2	0.088
Preoperative MLK score, median (IQR)	6.0 (4.0–8.0)	6.5 (4.5–10.0)	0.293
Postoperative 1-year MLK score, median (IQR)	1.0 (0.5–4.0)	3.0 (1.0–6.0)	0.168
Preoperative LM score, median (IQR)	14.0 (9.0–18.0)	16.0 (13.0–18.5)	0.617
Allergic status, n (%)	36 (67.9%)	9 (75.0%)	0.763
Asthma, n (%)	6 (11.3%)	4 (33.3%)	0.058
Current smoking, n (%)	8 (15.1%)	6 (50.0%)	0.009 [a]
Serum WBC counts (1000/μL), median (IQR)	7.9 (5.8–10.5)	10.9 (9.1–14.4)	0.009 [a]
Serum ECP (μg/L), median (IQR)	15.0 (7.1–35.8)	37.9 (20.3–54.1)	0.021 [a]
Serum total IgE (kU/L), median (IQR)	191.5 (102.3–442.8)	183.0 (76.6–516.0)	0.931
Serum eosinophil counts (/μL) , median (IQR)	171.2 (92.6–349.9)	217.4 (53.9–484.3)	0.478
Preoperative SNOT-22 score, median (IQR)	46 (35.0–67.5)	61 (44.3–68.5)	0.141
Postoperative 1-year SNOT-22 score, median (IQR)	15.0 (6.0–23.0)	41.0 (25.0–54.5)	0.001 [a]

[a] Statistically significant. T2, type 2; CRS, chronic rhinosinusitis; ECP, eosinophil cationic protein; IgE, immunoglobulin E; IQR, interquartile range; WBC, white blood cell count; MLK, modified Lund-Kennedy; LM, Lund-Mackay.

Table 3. Logistic regression analysis for postoperative uncontrolled CRS in the T2 CRS group.

Parameters	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Age	1.0 (0.9–1.0)	0.931		
Gender	0.3 (0.1–1.3)	0.102		
Preoperative MLK score	1.1 (0.9–1.4)	0.289		
Preoperative LM score	1.0 (0.9–1.2)	0.616		
Allergic status	1.3 (0.3–5.3)	0.761		
Asthma	3.9 (0.9–17.0)	0.069		
Current smoking	5.5 (1.4–21.4)	0.014 [a]	4.5 (0.9–22.4)	0.071
Serum WBC counts	1.3 (1.1–1.5)	0.014 [a]	1.3 (1.0–1.6)	0.042 [a]
Serum ECP level	1.0 (1.0–1.1)	0.019 [a]	16.7 (1.7–161.6)*	0.015 [a]
Serum total IgE level	1.0 (0.9–1.0)	0.778		
Serum eosinophil counts	1.0 (0.9–1.0)	0.518		

[a] Statistically significant. *The cut-off level of serum ECP ≥ 17.0 μg/L was applied to perform multivariate logistic regression analysis. T2, type 2; CRS, chronic rhinosinusitis; ECP, eosinophil cationic protein; IgE, immunoglobulin E; IQR, interquartile range; WBC, white blood cell count; MLK, modified Lund-Kennedy; LM, Lund-Mackay.

patients presented with nasal polyps and 4 patients presented with only purulence. Current smoking, serum white blood cell counts, and serum ECP levels were found to be associated with patients with postoperative uncontrolled CRS (p = 0.009, 0.009, and 0.021, respectively; Table 2). Multivariate logistic regression analysis showed that a higher serum ECP level and a higher WBC count were significant factors related to postoperative uncontrolled CRS (Table 3). When we further applied variance inflation factor (VIF) to test if there were any collinearity between serum ECP levels and WBC counts, the final VIF showed around 1 point,

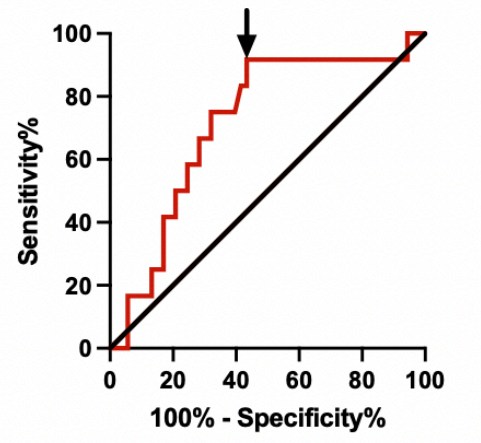

Figure 1. Receiver operating characteristic curve analysis of serum ECP level to predict the postoperative uncontrolled CRS in T2 CRS group. Data revealed the optimal cut-off level of serum ECP was 17.0 µg/L, attaining a sensitivity of 91.7% and a specificity of 56.6%. T2, type 2; CRS, chronic rhinosinusitis; ECP, eosinophil cationic protein.

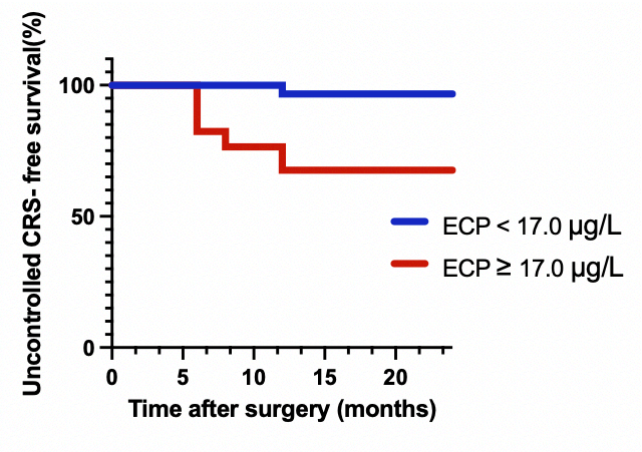

Figure 2. Kaplan-Meier curve estimates for postoperative uncontrolled among T2 CRS patients with preoperative serum ECP < 17.0 µg/L vs those with ≥ 17.0 µg/L. The uncontrolled rate was significantly higher in patients with preoperative serum ECP ≥ 17.0 µg/L. T2, type 2; CRS, chronic rhinosinusitis; ECP, eosinophil cationic protein.

indicating there was no correlation between these parameters. We further determined the optimal cut-off value of the serum ECP level to predict postoperative uncontrolled CRS using ROC curve analysis. According to Youden's index, we obtained a sensitivity of 91.7% and specificity of 56.6% with serum ECP levels of 17.0 µg/L (area under the ROC curve = 0.715, p = 0.021; Figure 1). For the T2 CRS group with preoperative serum ECP levels of more than 17.0 µg/L, there was a 16.7-fold risk for postoperative uncontrolled CRS (Table 3). By applying the cut-off value of the ECP levels at 17.0 µg/L, we obtained a positive predictive value of 32.3% (11 of 34) and a negative predictive value (NPV) of 96.8% (30 of 31) for the prediction of postoperative uncontrolled CRS. Furthermore, as a continuous variable, the risk of postoperative uncontrolled CRS increased by 3.1% for each 1 µg/L increase in serum ECP concentration.

Uncontrolled disease in the non-T2 CRS group

Among patients with uncontrolled CRS in this group, there were 2 with only purulence, 2 with only nasal polyps and another one patient presented with both purulence and nasal polyps. When univariate logistic regression analysis was applied in this group, the results showed there were no parameters statistically significantly related to postoperative uncontrolled CRS (Table 4).

Uncontrolled disease-free analysis

Figure 2 shows the postoperative uncontrolled CRS analysed using the Kaplan–Meier survival curve in the T2 CRS group. Patients were divided according to the cut-off value of serum ECP levels of 17.0 µg/L obtained from the ROC curve analysis, and the survival rate from postoperative uncontrolled CRS was significantly different (p = 0.003, log-rank test). Cox proportional hazard regression analysis revealed that the HR of patients with T2 CRS with ECP levels ≥ 17.0 µg/L resulted in postoperative uncontrolled CRS of 11.3 (95% CI, 1.5 to 87.3; p = 0.020). Furthermore, among the patients with postoperative uncontrolled CRS in the T2 group, most (11 of 12, 91.7%) occurred within 1 year after surgery. Accordingly, patients with T2 CRS with ECP levels ≥ 17.0 µg/L would have an HR of 11.3, resulting in uncontrolled CRS in the early postoperative period.

Discussion

A previous study has suggested that serum ECP concentration is associated with the degree of chronic inflammation and may be useful for estimating the prognosis of CRS under a 6-month follow-up [23]. In our previous investigation, measurement of serum ECP levels was easy and fast and could be used to provide a preoperative prediction of the surgical prognosis for patients with CRSwNP within the first postoperative year [18]. In that study, CRSwNP patients with serum ECP levels ≥21.8 µg/L would have an HR of 7.6 to have an early postoperative recurrence. In the current study, we found that patients with T2 CRS with preoperative serum ECP levels ≥ 17.0 µg/L had a 16.7-fold risk of postoperative recurrence. Most uncontrolled status in T2 CRS (91.7%) occurred within the first year after surgery. This correlation was not observed in those with non-T2 CRS. Accordingly, preoperative serum ECP level could serve as a powerful independent biomarker for early postoperative uncontrolled disease in patients with T2 CRS, and patients with a high preoperative serum ECP levels should be monitored intensively, especially in the first postoperative year. Current smoking and asthma have been documented to be related to recurrence after surgery [24,25]. For patients with T2 CRS, under the multivariate regression model,

Table 4. Comparison between the patients without and with postoperative uncontrolled CRS groups with univariate logistic regression analysis in non-T2 CRS.

Parameters	Without uncontrolled CRS group (n=43)	With uncontrolled CRS group (n=5)	p-value	Univariate analysis	
				Odds ratio (95%CI)	p-value
Age (years), median (IQR)	44.0 (34.0–59.0)	50.0 (49.0–59.5)	0.511	1.0 (0.9–1.1)	0.400
Gender (male: female)	27:16	1:4	0.069	6.7 (0.7–65.8)	0.100
Preoperative MLK score, median (IQR)	6.0 (4.0–10.0)	3.0 (2.0–12.0)	0.670	0.9 (0.8–1.2)	0.824
Preoperative LM score, median (IQR)	11.0 (8.0–20.0)	6.0 (4.0–118.5)	0.260	0.9 (0.8–1.0)	0.383
Allergic status, n (%)	6 (13.9%)	0 (0%)	0.364	-	1.000
Asthma, n (%)	1 (2.3%)	0 (0%)	0.733	-	1.000
Current smoking, n (%)	7 (16.2%)	1 (20.0%)	0.838	1.3 (0.1–13.2)	0.623
Serum WBC counts (1000/μL), median (IQR)	8.9 (6.9–10.8)	7.7 (6.9–0.5)	0.490	0.9 (0.6–1.2)	0.527
Serum ECP (μg/L), median (IQR)	12.8 (5.6–19.3)	32.2(10.5–49.9)	0.137	1.0 (0.9–11.0)	0.356
Serum total IgE (kU/L), median (IQR)	32.4 (10.6–55.1)	50.6 (26.0–72.0)	0.322	1.0 (0.9–1.0)	0.777
Serum eosinophil counts (/μL) , median (IQR)	49.6 (9.4–88.8)	38.4 (9.3-166.0)	0.743	1.0 (0.9–11.0)	0.469

[a] Statistically significant. T2, type 2; CRS, chronic rhinosinusitis; WBC, white cell count; ECP, eosinophil cationic protein; IgE, immunoglobulin E; IQR, interquartile range; MLK, modified Lund-Kennedy; LM, Lund-Mackay.

high preoperative serum ECP levels and WBC counts were independent powerful risk factors associated with surgical outcomes The risk of postoperative uncontrolled CRS increased by 3.1% for each 1 μg/L increase in serum ECP concentration. Therefore, patients with T2 CRS with serum levels much higher than 17.0 μg/L should be reminded in advance of the risk of early postoperative uncontrolled disease while surgical treatment is scheduled.

In our previous study, the preoperative NPV of serum ECP levels at 21.8 μg/L indicated that patients with CRSwNP had a chance of 94.7% to remain disease-free within 1 year postoperatively if their serum ECP levels were below the cut-off value [18]. In this study, when these CRS patients were classified based on the phenotypes, there were 83 CRSwNP and 30 CRSsNP in this study. Among the patients with postoperative uncontrolled CRS, there were 12 in the CRSwNP group and 5 in the CRSsNP group. In this subgroup analysis, we further determined the optimal cut-off value of the serum ECP level to predict postoperative uncontrolled CRS using ROC curve analysis. According to Youden's index, we obtained a sensitivity of 83.3% and specificity of 73.2% with serum ECP levels of 25.0 μg/L in the CRSwNP group (area under the ROC curve = 0.802, $p < 0.001$). By applying this cut-off value of the ECP levels, we could further obtain a PPV of 37.9% and a NPV of 98.1% for the prediction of postoperative uncontrolled CRS, similar to our previous study(18). In the CRSsNP group, however, the serum ECP levels were not associated with postoperative uncontrolled CRS. For the pattern of endotype-directed treatment for CRS, in this current investigation, the NPV of preoperative serum ECP levels at 17.0 μg/L indicated that preoperative serum ECP levels lower than the cutoff levels may bring a possibility of 96.8% to remain without uncontrolled CRS after surgical treatment for patients with T2 CRS. This prediction model is not feasible for the non-T2 CRS group. Consequently, the high NPV of preoperative serum ECP levels in predicting uncontrolled CRS after surgery is noteworthy for both phenotype and endotype analyses. In the case of CRSwNP or T2 CRS patients with preoperative serum ECP levels below the established threshold, we can reasonably anticipate better disease control following surgical intervention. Notably, the study revealed that the cut-off value for serum ECP levels, when applied to endotype analysis, was even lower. This suggests when we discuss how a lower serum ECP level correlates with a better postoperative disease control, the criteria are more stringent when considering endotype analysis. In the era of endotype-driven management and patient-centred assessment for CRS, we may provide preoperative consultation for surgical outcomes in advance based on the serum ECP levels for patients with T2 CRS whose medical treatment has failed. For patients with T2 CRS, high preoperative serum ECP levels may help alert physicians and patients regarding the possibility of early postoperative uncontrolled CRS in advance. Alternative treatments, including biologics, may be considered for patients with T2 CRS with high serum ECP levels before the initiation of surgical plans. Nevertheless, a low serum ECP level still cannot guarantee a long-term outcome, and a long follow-up period would be critical for a more definite conclusion.

In patients with non-T2 CRS, no single powerful factor was found to be associated with postoperative uncontrolled CRS in the regression analysis. This may be owing to the relatively

smaller sample size and fewer patients with uncontrolled CRS (five of 48, 10.4%, respectively) in the non-T2 group. Elevation in serum ECP levels has also been documented in non-T2 immune response-associated diseases, such as bacterial or viral infections, bacterial sinusitis, chronic obstructive pulmonary disease, tuberculosis, and drug-induced acute respiratory distress syndrome (ARDS)[26-28]. ECP was generally considered a marker of eosinophil activity that might be useful in assessing the severity of allergic inflammation in the nasal or bronchial mucosa [24]. In our study, serum ECP levels had a weak correlation with eosinophil counts in peripheral blood ($p = 0.081$) in the T2 CRS group but not in the non-T2 group ($p = 0.448$). ECP has also been detected in other leukocytes, such as neutrophils and white blood cell populations devoid of eosinophils [24]. This might be the reason that eosinophils are probably not the only source of the detected serum ECP and would explain the distinct characteristics of nasal polyps in Asian patients. In a recent study, Kim et al. suggested that neutrophils may also contribute to disease refractoriness in CRSwNP in the Asian population [29]. In the future, we should further investigate the correlation between tissue eosinophil counts, tissue ECP levels, and neutrophil markers in the uncontrolled CRS group of patients with CRS of every endotype to identify their roles in the surgical outcome.

This study was limited by the patient source from a single institution of a referral centre and a single surgeon, which may not be generalizable to all populations and selection bias may exist. Under the COVID-19 pandemic, the relatively small number of cases that fulfilled postoperative visits and assessments is another limitation. More patients and a relatively longer follow-up duration are needed to draw further conclusions.

Conclusion

Serum ECP levels could serve as a feasible prognostic biomarker for T2 but not for patients with non-T2 CRS after surgery. This study showed that patients with T2 CRS with a preoperative serum ECP levels <17.0 μg/L would have a 96.8% chance to a have better disease control. A 16.7-fold risk for early postoperative uncontrolled CRS would be expected for patients with T2 CRS if their preoperative serum ECP is above the cut-off level, and the risk would increase by 3.1% for each 1 μg/L increase in serum ECP level. For patients with T2 CRS, high preoperative serum ECP levels may help alert physicians and patients regarding the possibility of early postoperative uncontrolled CRS in advance, and alternative treatments may be considered.

Conflicts of interest

The authors have no competing interests to declare.

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Authors' contributions

TJL, PHC and CHF collected and analysed data, and prepared the manuscript; PCT, TJL, PHC and CHF completed image processing and participated in data discussion; PCT, PHC and CHF designed the study, interpreted data, and prepared the manuscript.

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