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ORIGINAL RESEARCH

Risk Factors of Postoperative Residual Sinus Inflammation in Patients with Eosinophilic Chronic Rhinosinusitis and Nasal Polyps

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Purpose: The combination of surgery and biologics may be required for patients with severe eosinophilic chronic rhinosinusitis with nasal polyps (CRSwNP) and a high inflammatory burden. This study aimed to identify the risk factors for postoperative residual sinus inflammation in patients with eosinophilic CRSwNP.

Methods: Adult patients with bilateral CRSwNP planning to undergo endoscopic sinus surgery were prospectively recruited. Their clinical information, computed tomography images, and tissue eosinophil count were evaluated. Postoperative residual mucosal inflammation was defined as a modified Lund-Kennedy endoscopy score of ≥5 at three months postoperatively.

Results: The study included 143 adult patients with bilateral CRSwNP. Ninety-three patients (65.0%) had eosinophilic CRSwNP based on tissue eosinophil counts of ≥10/high power field. Twenty-six patients (28.0%) with eosinophilic CRSwNP experienced postoperative residual sinus inflammation. The prevalence of comorbid asthma, nasal polyp score, Lund-Mackay score, ethmoid/maxillary ratio, olfactory cleft opacification score on computed tomography images, serum eosinophil cationic protein level, and tissue eosinophil count were significantly higher in the patients with than in those without postoperative residual sinus inflammation (all $p<0.05$). A nomogram was constructed to predict the probability of experiencing post-op residual sinus inflammation.

Conclusion: Comorbid asthma, nasal polyp score, Lund–Mackay score, ethmoid/maxillary ratio, and olfactory cleft opacification score are significant predictors of postoperative residual sinus inflammation in patients with eosinophilic CRSwNP. Clinicians can use a nomogram based on these factors to predict therapeutic outcomes after sinus surgery and the need for postoperative adjuvant therapy such as biologics.

Plain Language Summary: The combination of surgery and biologics may be required for patients with severe eosinophilic chronic rhinosinusitis with nasal polyps (CRSwNP) and a high inflammatory burden. This study included 143 adult patients with bilateral CRSwNP. Ninety-three patients (65.0%) had eosinophilic CRSwNP. Comorbid asthma, nasal polyp score, Lund–Mackay score, ethmoid/maxillary ratio, and olfactory cleft opacification score are significant predictors of postoperative residual sinus inflammation in patients with eosinophilic CRSwNP. Clinicians can use a nomogram based on these factors to predict therapeutic outcomes after sinus surgery and the need for postoperative adjuvant therapy such as biologics.

Keywords: chronic rhinosinusitis, eosinophil, endoscopic sinus surgery, Lund-Mackay score, modified Lund-Kennedy endoscopy score, nasal polyp

Introduction

Chronic rhinosinusitis (CRS) is characterized by persistent sinonasal inflammation, nasal purulent discharge, and nasal blockage for more than 12 weeks.[1,2] CRS is divided into CRS without nasal polyps or with nasal polyps (CRSwNP),

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according to whether nasal polyps are present or not.[3] CRSwNP in Western countries is characterized by type 2 skewed eosinophilic inflammation, which involves the activation of type 2 helper T cell and innate lymphoid cell and increased expressions of interleukin (IL)-4, IL-5, IL-13, and eosinophil cationic protein (ECP).[4]

Eosinophilic inflammation is significantly less prevalent in patients with CRSwNP in Asia than in the Western countries. Type 2 skewed eosinophilic inflammation occurs in 40–60% of patients with CRSwNP in Japan and East Asia, which is markedly lower than the rate of 80% in Western countries.[5–7] However, the prevalence of CRSwNP with eosinophilic infiltration has been increasing in Asia in recent years due to the Westernization of eating habits and environments.[8]

Endoscopic sinus surgery (ESS) for CRSwNP refractory to medical treatment has been largely reported to be effective and safe.[9] However, patients with a high inflammatory burden and severe nasal polyposis have a recurrence rate of 40% in general and up to 60% for those with comorbid asthma after ESS.[10,11] Patients with CRSwNP with severe type 2 eosinophilic inflammation usually experience poorer improvement after surgical intervention, have persistent post-operative (post-op) mucosal inflammation, and are more susceptible to recurrence after surgery.[12,13]

The role of type 2 eosinophilic inflammation in disease severity, recurrence, and comorbidity in CRS has been recognized. Therefore, several biologics targeting IL-4, IL-5, IL-13 and immunoglobulin E (IgE) have been administered, and patients with severe uncontrolled CRSwNP have demonstrated good response in clinical trials and real world clinical practice.[14,15] A previous study revealed that patients undergoing ESS achieved a higher reduction of nasal polyp size, while those receiving biologics (Dupilumab, anti-IL-4 α receptor) experienced a higher improvement in the quality of life and smell measurement in CRSwNP.[16,17] Sinus surgery can remove sinonasal inflammatory content, open the drainage pathway of sinuses immediately, and relieve patient symptoms early.[16] However, biologics targeting type 2 inflammatory mediators can suppress tissue inflammation, restore the epithelial barrier, and resolve post-op residual sinonasal inflammation.[17,18] As a result, a combination of surgery and biologics may be required for patients with severe type 2 eosinophilic CRSwNP and a high inflammatory burden to achieve optimal therapeutic outcomes.[18–20]

Thus, this study aimed to evaluate and identify the risk factors for post-op residual sinus inflammation in patients with eosinophilic CRSwNP after ESS. Patients with type 2 eosinophilic CRSwNP and poor response to ESS would benefit from biologic therapy targeting mediators in type 2 inflammation. This can help clinicians to promptly identify patients with poor surgical response and provide additional treatment to achieve optimal therapeutic outcomes in patients with eosinophilic CRSwNP.

Materials and Methods

Patients

After approval by the Institutional Review Board of Chang Gung Memorial Hospital (IRB numbers: 202002219A3, 202102257A3, and 202202075A3), adult patients (≥18 years) who planned to undergo ESS for bilateral CRSwNP were prospectively enrolled after providing signed informed consent from November 2020 to December 2023 (Figure 1). All procedures were conducted in accordance with the relevant ethical guidelines and regulations, and the Declaration of Helsinki. Previous studies collected preoperative data to evaluated the relationship between clinical markers and tissue type 2 inflammatory severity,[7] to characterize the clinical features of patients with comorbid asthma,[21] and to investigate the predictive value of the ethmoid-to-maxillary (E/M) ratio based on different CT scoring systems in patients with CRSwNP.[22] In the current study, we collected the postoperative data to identify the risk factors for residual sinus inflammation after surgery in patients with eosinophilic CRSwNP.

CRSwNP was diagnosed according to the EPOS2020 definition.[2] The enrolled patients did not respond to three months of conservative medical therapies including intranasal corticosteroids and nasal douches. The presence of nasal polyps was confirmed based on endoscopic findings and histopathological analysis. We excluded patients (a) with sinonasal tumor; (b) having concomitant disorders of immunologic complications, cystic fibrosis, or primary ciliary dyskinesia; and (c) received treatment with oral corticosteroids, monoclonal antibodies, or immunosuppressives before enrolment (e) declined to participate.

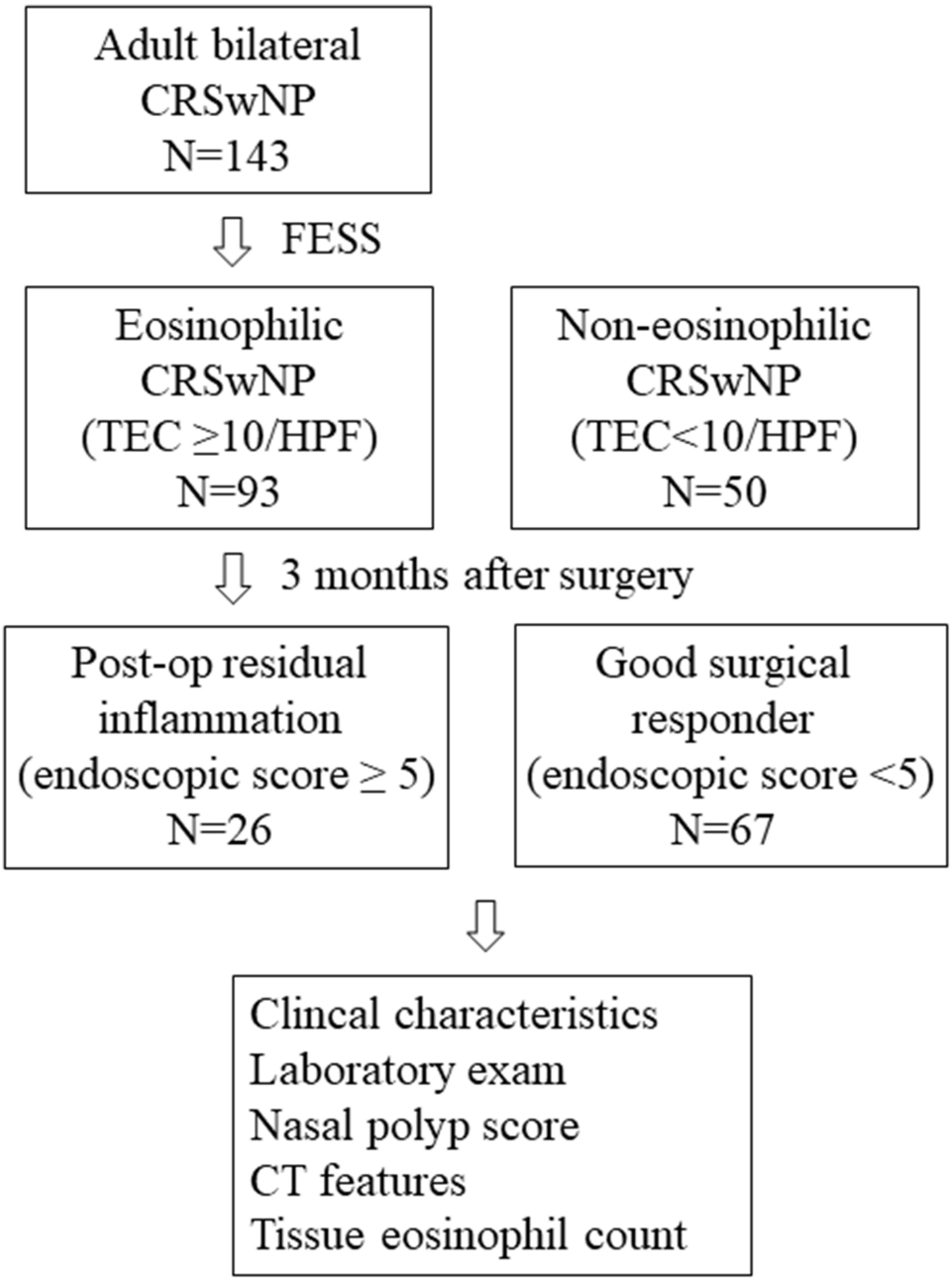

Figure 1 Algorithm for enrollment of study cohorts. Residual sinus inflammation was defined by modified Lund-Kennedy endoscopic score ≥ 5.
Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyp; FESS, functional endoscopic sinus surgery; TEC, tissue eosinophil count; HPF, high power field; post-op, postoperative; CT, computed tomography.

Clinical information of the participants, including relevant clinical symptoms, medical history of allergy and comorbid asthma, cigarette smoking, and associated laboratory and image surveys were collected. Allergy was determined using an automated immunoassay (ImmunoCap) to detect serum specific IgE antibodies to the aeroallergens.[7] Comorbid asthma was confirmed based on fulfillment of the diagnostic criteria of the Global Initiative for Asthma guidelines and the regular use of inhaled corticosteroids.[23] The sinonasal outcome test- 22 (SNOT-22) was used to assess the nasal symptoms and quality of life.[24] Each item in the SNOT-22 was scored from 0 to 5 (from no problem to worse), with a total score of up to 110. Laboratory examinations included peripheral blood cell counts, serum total IgE, and ECP concentrations.

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All participants underwent bilateral ESS targeting the sinuses, including maxillary, anterior and posterior ethmoid, frontal, and sphenoid sinuses. Sphenoidotomy was performed depending on the presence or absence of sinus opacification on computed tomography (CT) images. After surgery, the participants subsequently received standard post-op care, encompassing antibiotic therapy with Curam 875/125 mg/tab (Amoxicillin + clavulanic acid, SANDOZ GMBH, Aus) for 3 weeks, intranasal corticosteroids, nasal douches, and weekly follow-ups in the first month and monthly for the subsequent two visits. At 3 months after surgery, some patients experienced good response but some exhibited residual sinus inflammation on nasal endoscopic evaluation (Figure 2).

Nasal Endoscopic Evaluation

The nasal polyp scoring (NPS) system was used as described previously.[25] The polyps were assessed using nasal endoscopy and graded as follows: no polyps (score 0); small polyps in the middle meatus (score 1); polyps reaching below the lower border of the middle turbinate (score 2); polyps medial to the middle turbinate or reaching the lower border of the inferior turbinate (score 3); and large polyps with total obstruction of the inferior meatus (score 4). The modified Lund-Kennedy (MLK) endoscopic scoring system based on the degree of edema, polyps, and discharge was used to evaluate the severity of post-op sinus mucosal inflammation.[26] Post-op residual mucosal inflammation was defined as a MLK score of ≥ 5 at three months after surgery according to previous studies (Figure 2).[26,27] All patients provided informed consent before participating in the study. All study procedures were performed according to relevant guidelines and regulations.

Tissue Eosinophil Count Quantification

Polyp specimen collected during sinus surgery was fixed in formalin and embedded in paraffin. Standard 5-μm sections underwent haematoxylin and eosin staining. Tissue eosinophils were counted at ×400 magnification (high power field, HPF) microscopic evaluation in three fields with most severe inflammatory cell infiltration and intact mucosal epithelium. Eosinophilic CRSwNP was defined as a tissue eosinophil count of ≥ 10/HPF.[2]

Sinonasal Computed Tomographic Evaluation

The sinonasal CT images with one section per mm were independently reviewed by two experienced rhinologists. The Lund-Mackay score (LMS) was used to quantify CRS severity radiologically.[28] As previously described, the maxillary sinus, anterior and posterior ethmoidal sinuses, frontal sinus, sphenoid sinus, and ostiomeatal complex were assigned scores of 0, 1, or 2 (indicate no abnormality, partial or complete opacification), respectively. The ostiomeatal complex was assigned scores of 0 or 2 (indicating the presence or absence of obstruction). The total score was up to 24 bilaterally.

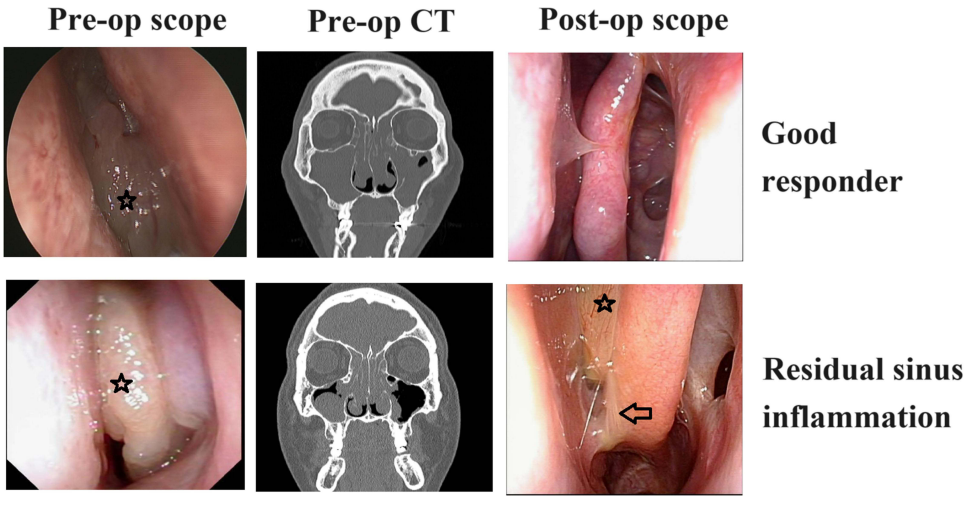

Figure 2 Representative computed tomographic images and perioperative endoscopic evaluations in patients with bilateral CRSwNP. Star: nasal polyp; arrow: mucoid discharge.

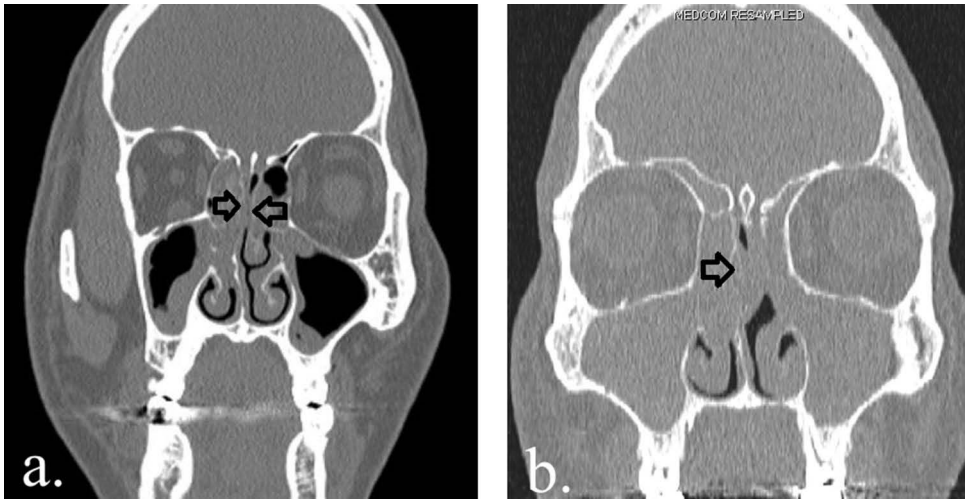

Figure 3 The olfactory cleft opacification on the computed tomography (CT) image (arrow) was graded using a scale of 0–3 indicating clear (score 0), less than half ((**a**) left nose, score 1), more than half ((**b**) right nose, score 2), and total ((**a**) right nose, score 3) opacification at each side of the olfactory cleft (the area between the middle turbinate and the nasal septum on the coronal plane section of the cribriform plate's CT imaging).

The E/M ratio was determined by calculating the ratio of the average scores for the anterior and posterior ethmoid sinuses to that of the maxillary sinuses on CT images.[29,30] A higher disease involvement in the ethmoid sinus area and central sinonasal compartment was associated with a higher E/M ratio.

The olfactory cleft opacification score was evaluated on a scale of 0–3 indicating clear, less than half, more than half, or total opacification on each side of the olfactory cleft on CT images respectively (Figure 3).[7,31]

Statistical Analyses

The data were statistically analysed using GraphPad Prism 5 (GraphPad Prism Software, Inc., San Diego, Calif, USA), SPSS (version 27.0; SPSS Inc., Chicago, IL) and RStudio v2022.02.1 (RStudio, Boston, MA, USA). D'Agostino & Pearson omnibus normality test was used to evaluate the normality of data. Categorical variables were compared using the x^2 test or Fisher's exact test as appropriate. Continuous variables were compared using the Mann–Whitney *U*-test or *t* test. Regression analyses were used to assess the association between post-op residual sinus inflammation and clinical variables. R-squared (R^2) was used to assess the model fit. To identify the cut-off values for the prediction of residual sinus inflammation in eosinophilic CRSwNP, receiver operating characteristic (ROC) curves were generated and the area under the ROC curve (AUC) was evaluated. Based on the results of the logistic regression analysis, a nomogram model was developed to predict the risk of post-op residual sinus inflammation. In the nomogram, each variable was assigned a score. The total points were derived by calculating the sum of the corresponding scores from the five variables, reflecting the predicted probability of post-op residual sinus inflammation in eosinophilic CRSwNP for an individual. The ROC curve and AUC were used to evaluate the predictive performance of the nomogram model. Statistical significance was set at $p < 0.05$.

Results

Clinical Characteristics of Patients

A total of 143 adult patients with bilateral CRSwNP were enrolled and evaluated. Ninety-three (65.0%) had eosinophilic CRSwNP (tissue eosinophil count ≥ 10/HPF). Twenty-six of the 93 (28%) patients with eosinophilic CRSwNP experienced post-op residual sinus inflammation defined by a post-op MLK score of ≥ 5 within three months after surgery. The demographic data of the patients with eosinophilic CRSwNP are shown in Table 1. The prevalence of comorbid asthma, NPS, LMS, E/M ratio, olfactory cleft opacification score on CT image, serum ECP level, and tissue eosinophil count were significantly higher for the patients with than for those without post-op residual sinus inflammation (all $p < 0.05$). The maxillary, anterior and posterior ethmoid, and frontal sinuses of all participants were drained and re-

Table 1 Clinical Characteristics of Participants with Eosinophilic Chronic Rhinosinusitis with Nasal Polyp

	Total	Post-Op Residual Inflammation	Good Responder	P value[†]
Number	93 (100.0%)	26 (28.0%)	67 (72.0%)	
Age (years)	47.5 ± 13.4	50.2 ± 12.9	46.5 ± 13.5	0.219
Female:male	32:61	9:17	23:44	0.979
Comorbid asthma	24 (25.8%)	12 (46.2%)	12 (17.9%)	0.005**
NSAID/aspirin intolerance	5 (5.4%)	4 (15.4%)	1 (1.5%)	0.021*
Allergy	52 (55.9%)	15 (57.7%)	37 (55.2)	0.509
Smoking	18 (19.4%)	3 (11.5%)	15 (22.4%)	0.235
Previous sinus surgery	32 (34.4%)	10 (38.5%)	22 (32.8%)	0.608
SNOT-22	48.6 ± 19.2	49.8 ± 12.3	48.2 ± 21.3	0.529
Nasal polyp score	5.4 ± 1.6	5.9 ± 1.4	5.2 ± 1.7	0.033*
CT Lund-Mackay score	16.9 ± 4.1	18.2 ± 3.6	16.4 ± 4.2	0.036*
CT ethmoid/maxillary ratio	1.2 ± 0.4	1.4 ± 0.4	1.2 ± 0.4	0.021*
CT olfactory cleft opacification score	4.3 ± 1.9	4.9 ± 1.8	4.0 ± 1.9	0.018*
Serum IgE (KU/L)[a]	123.5 (215.3)	144.0 (263.2)	120.0 (203.1)	0.377
Serum ECP (μg/L)	45.1 ± 51.5	62.71 ± 58.5	38.4 ± 47.4	0.039*
WBC (1000/uL)	7.3 ± 1.7	6.9 ± 1.6	7.4 ± 1.8	0.312
Neutrophil (%)	59.2 ± 8.8	59.5 ± 8.2	59.1 ± 9.1	0.550
Lymphocyte (%)	29.3 ± 7.1	28.8 ± 6.2	29.5 ± 7.5	0.290
Eosinophil (%)	5.1 ± 4.2	5.5 ± 4.3	4.9 ± 4.1	0.394
BEC (/uL)[a]	301.3 (355.1)	297.7 (325.2)	301.3 (359.2)	0.480
Tissue eosinophil count (/HPF)	67.8 ± 63.2	83.6 ± 66.0	61.7 ± 61.7	0.033*

Notes: Data are represented as mean ± stand deviation. [†]Comparison between the participants with and without postoperative (post-op) residual sinus inflammation (defined by modified Lund-Kennedy endoscopic score ≥ 5) was performed using the Mann–Whitney *U*-test for continuous variables and chi-square test or Fisher exact test for categorical variables. [a]Data failing the normality test are represented as median (interquartile range). *p < 0.05, **p < 0.01.

Abbreviations: NSAID, non-steroidal anti-inflammatory drugs-exacerbated respiratory disease; SNOT-22, sinonasal outcome test-22; CT, computed tomography; E/M ratio, ethmoid/maxillary ratio; IgE, immunoglobulin E; ECP, eosinophil cationic protein; WBC, white blood cell; BEC, blood eosinophil count; HPF, high power field.

ventilated. The rate of sphenoidotomy was not significantly different between patients with and without post-op residual sinus inflammation (84.6% vs 70.1%, p=0.244).

Regression Analyses

Table 2 shows the associations between the clinical variables and post-op residual sinus inflammation examined using logistic regression analysis. Univariate regression analysis showed that comorbid asthma, NPS, E/M ratio, and olfactory cleft opacification score on CT image were significant predictors of post-op residual sinus inflammation in patients with eosinophilic CRSwNP. Only comorbid asthma maintained a statistically significant association in the multivariate analysis.

ROC Curve Analysis

ROC curves were plotted, and AUC values were calculated to evaluate the sensitivity and specificity of comorbid asthma, NPS, LMS, the E/M ratio, and olfactory cleft opacification score on CT image for predicting post-op residual sinus inflammation in patients with eosinophilic CRSwNP (Figure 4). The AUC was 0.641 for asthma (p = 0.035), 0.606 for NPS (p = 0.114), 0.620 for LMS (p = 0.073), 0.653 for E/M ratio (p = 0.023), and 0.651 for the olfactory cleft opacification score (p = 0.024).

Table 2 Logistic Regression Analyses of Clinical Variables for Residual Sinus Inflammation After Surgery[†]

Variables	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
Age	1.02 (0.99–1.06)	0.241		
Gender	1.01 (0.39–2.63)	0.979		
Comorbid asthma	3.93 (1.46–10.60)	0.007**	3.19 (1.07–9.53)	0.037*
Smoking	0.44 (0.12–1.68)	0.232		
Previous sinus surgery	1.28 (0.50–3.27)	0.609		
SNOT-22	1.00 (0.98–1.03)	0.712		
Nasal polyp score	1.34 (0.98–1.84)	0.041*	1.30 (0.90–1.90)	0.167
Lund-Mackay score	1.12 (0.99–1.27)	0.052	1.01 (0.87–1.18)	0.866
E/M ratio	4.19 (1.16–15.21)	0.017*	2.92 (0.67–12.66)	0.152
Olfactory cleft opacification score	1.34 (1.01–1.79)	0.043*	1.10 (0.80–1.51)	0.577
Serum IgE (KU/L)	1.00 (1.00–1.00)	0.220		
Serum ECP (μg/L)	1.01 (1.00–1.02)	0.206		
BEC (/uL)	1.00 (1.00–1.00)	0.619		
Tissue eosinophil count (/HPF)	1.01 (1.00–1.01)	0.112		

Notes: *p < 0.05, **p < 0.01. [†]Endoscopic modified Lund-Kennedy score ≥ 5; R^2=0.207.
Abbreviations: CI, confidence interval; SNOT-22, sinonasal outcome test-22; E/M ratio, ethmoid/maxillary ratio; IgE, immunoglobulin E; ECP, eosinophil cationic protein; BEC, blood eosinophil count.

Nomogram for Predicting Post-Op Residual Sinus Inflammation

Given that the ROC analysis revealed absence of a single ideal predictor, a nomogram was constructed to predict the probability of post-op residual sinus inflammation in eosinophilic CRSwNP based on the results of the logistic regression analysis (Figure 5). The AUC of the nomogram was 0.747 (95% confidence interval, 0.708–0.804).

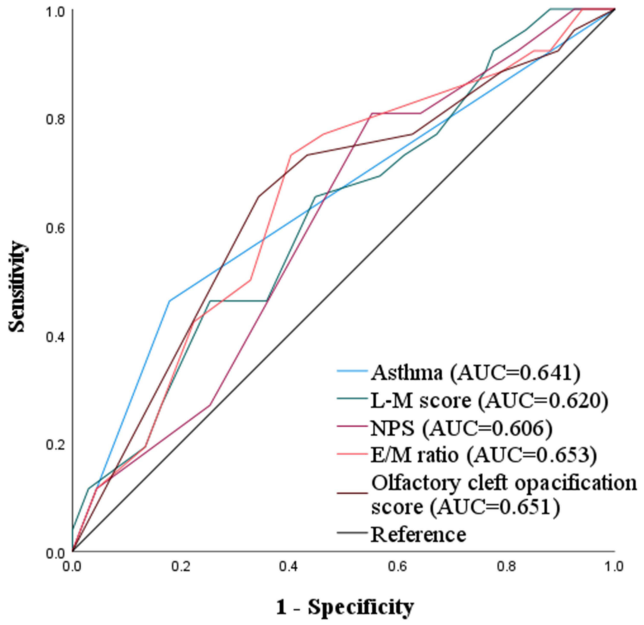

Figure 4 Receiver operating characteristic curves of comorbid asthma (p = 0.035), nasal polyp score (NPS; p = 0.114), Lund-Mackay (L-M) score (p = 0.073), ethmoid/maxillary sinus (E/M) ratio (p = 0.023), and olfactory cleft opacification score (p = 0.024) were used to detect the probability of post-op residual sinus inflammation in patients with eosinophilic CRSwNP.
Abbreviation: AUC, area under curve.

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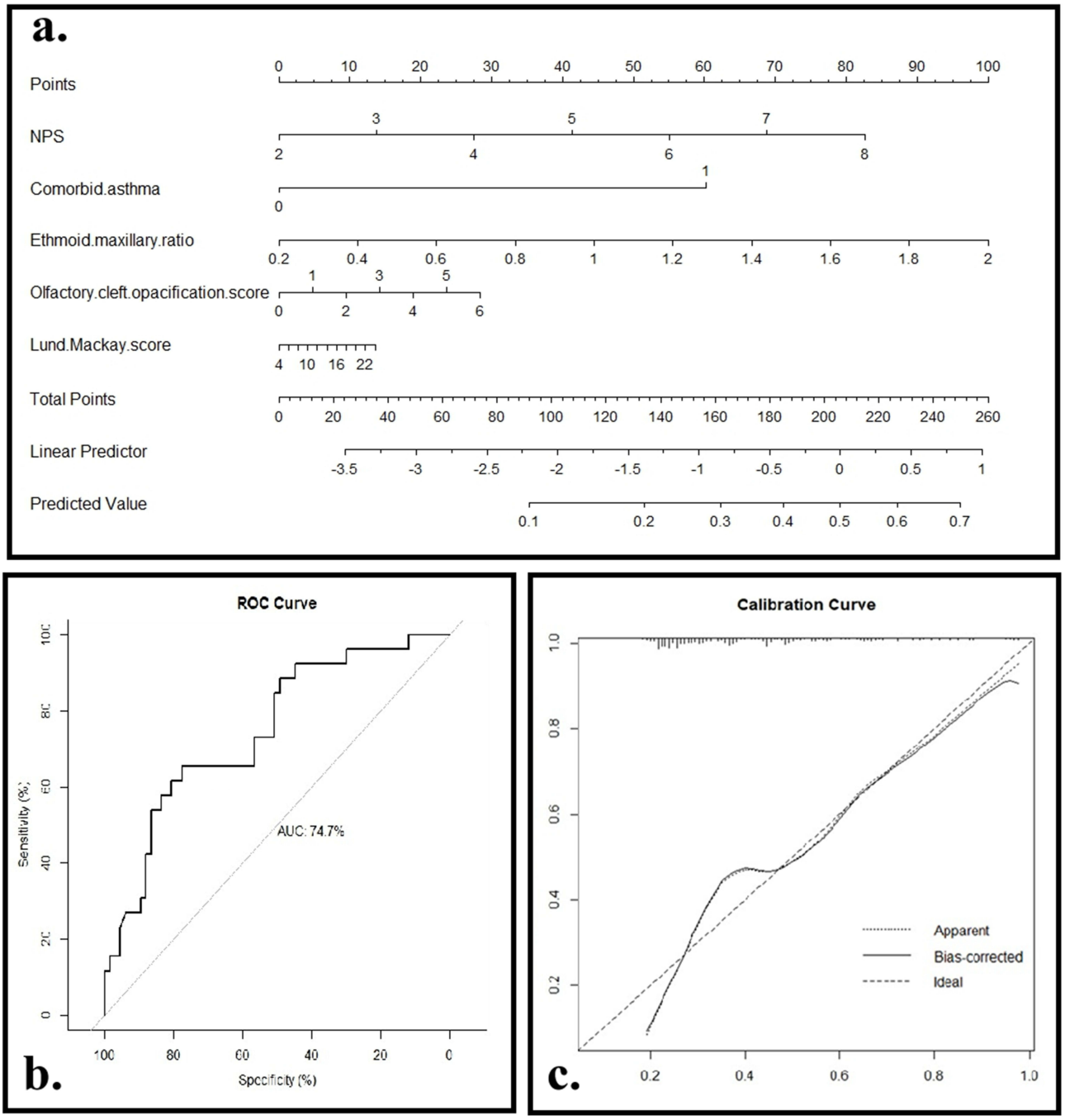

Figure 5 A nomogram developed to predict the probability of post-op residual sinus inflammation in patients with eosinophilic CRSwNP according to the results of the logistic regression analysis (**a**). In the nomogram, each value of a variable represents its score. The total points can be obtained by adding the corresponding scores from the five predictors, and the predicted value of post-op residual sinus inflammation for an individual can be indicated. Receiver operating characteristic (ROC) curve (**b**) and calibration curve (**c**) of the nomogram model for predicting the probability of post-op residual sinus inflammation in eosinophilic CRSwNP was plotted. The area under the ROC curve (AUC) was 0.747 (95% confidence interval = 0.708–0.804). The Ideal line represents the ideal model which predicted probabilities perfectly matching the actual probabilities. The Apparent line and the Bias corrected line respectively represent the nomogram model before and after bootstrap re-sampling method.
Abbreviation: NPS, nasal polyp score.

Discussion

ESS has been an effective strategy for treating CRSwNP, but patients with a high inflammatory burden and extensive nasal polyposis have a risk of recurrence of 40% in general and up to 60% when there is comorbid asthma.[9–11,32] Patients with CRSwNP with severe type 2 eosinophilic inflammation usually experience poorer improvement after surgical intervention, have persistent post-op mucosal inflammation, and have a greater susceptibility to recurrence after

surgery.[12] Several biologics targeting mediators in type 2 inflammation have been administered with good response in patients with severe uncontrolled CRSwNP.[15] Recent studies have revealed that patients who received adjuvant Dupilumab therapy had significantly better short-term sinonasal endoscopic scores than those who underwent only surgery, although both treatments were effective for symptom reduction.[18,20] Sinus surgery removed the sinonasal inflammatory contents and opened the drainage pathway of sinuses immediately, and biologics effectively suppressed the tissue inflammation, restored the epithelial barrier, and suppressed the post-op residual sinonasal inflammation.[16] Thus, patients with severe type 2 eosinophilic CRSwNP and a high inflammatory burden may require a combination of surgery and biologics to achieve optimal therapeutic outcomes.[18,20]

A recent study suggested that nasal endoscopy findings can be used to determine CRS disease control and treatment escalation.[33] The current study further evaluated the risk factors for post-op residual sinus inflammation (MLK score ≥ 5 on endoscopy evaluation) after ESS for patients with eosinophilic CRSwNP. The prevalence of comorbid asthma, NPS, LMS, E/M ratio, olfactory cleft opacification score on CT image, serum ECP level, and tissue eosinophil count were significantly higher for the patients with than for those without post-op residual sinus inflammation. Comorbid asthma, NPS, E/M ratio, and olfactory cleft opacification score on CT image were significant predictors of post-op residual sinus inflammation in regression analysis. Given the absence of a single ideal predictor in the ROC analysis, a nomogram was constructed to predict the probability of post-op residual sinus inflammation in eosinophilic CRSwNP based on the results of the regression analysis. This can help clinicians promptly identify patients with poor surgical response and benefits from adjuvant biological therapy and provide additional treatment to achieve optimal therapeutic outcomes in patients with eosinophilic CRSwNP.

Asthma is a common type 2 comorbid airway inflammation in eosinophilic CRSwNP based on the concept of a unified airway.[34] Comorbid asthma is a known indicator of more severe inflammation and a higher risk for postoperative recurrence of nasal polyps in patients with CRSwNP.[10,35,36] Similar to eosinophilic CRSwNP, comorbid asthma is less prevalent in Asia than in Western countries, which may be up to 60%.[6] In our study, comorbid asthma was found in only 25.8% of participants with eosinophilic CRSwNP and was still a strong predictive factor for those with post-op residual sinus inflammation. However, the sensitivity (46.2%) was not high due to the low prevalence. Simultaneous evaluation of other factors is necessary. Also, only five (5.4%) participants with eosinophilic CRSwNP had a history of aspirin or non-steroidal anti-inflammatory drugs (NSAID) intolerance in the present study, and all of them had comorbid asthma. Four of the patients exhibited post-op residual sinus inflammation. NSAID or aspirin-exacerbated respiratory disease in Chinese patients with CRSwNP is not as prevalent as that in Western countries, but it is still considered a predictive factor for severe eosinophilic CRSwNP and post-op residual sinus inflammation.[37,38]

NPS and LMS reflect the sinus inflammation burden by grading the polyp size and extent of sinus involvement. High NPS and LMS indicate a high inflammatory load and prolonged resolution of sinus inflammation, and it predict susceptibility to post-op residual sinus inflammation. Previous studies also reported that high NPS and LMS were indicators for poor surgical outcomes including polyp recurrence.[39–41]

Type 2 eosinophilic CRSwNP often involves the central sinonasal area, including ethmoid sinuses, middle turbinates, and the nasal olfactory cleft.[26,42] The mechanism underlying the predominant involvement of the central compartment in type 2 eosinophilic CRSwNP remains unclear. The possible explanations include the regional differences in molecular expression patterns within the sinonasal mucosa.[43,44] The Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis suggested a greater CT shadow of the ethmoid sinus than that of the maxillary sinus as one of the scoring criteria for eosinophilic CRS.[35] Meng et al demonstrated the E/M ratio as a predictor for differentiating adult eosinophilic from non-eosinophilic CRSwNP.[29] The current study showed that the E/M ratio and olfactory cleft opacification score on the CT image were associated with post-op residual sinus inflammation. These results indicated that the severity of type 2 eosinophilic inflammation is related to the post-op recovery of sinus mucosal inflammation. Further post-op adjuvant therapy may be required for severe eosinophilic CRSwNP. However, the E/M ratio and olfactory cleft opacification score on the CT image may be limited as type 2 eosinophilic inflammatory markers because the difference may diminish in patients with extensive disease involvement, such as those with total opacification in all sinuses (LMS 24).

The serum ECP concentration and tissue eosinophil count were significantly higher in patients with post-op residual sinus inflammation than in those without. However, they were not significant predictors of post-op residual sinus inflammation in the regression analysis. In the current study, we performed analysis only in patients with eosinophilic CRSwNP, and all these patients

had high ECP concentrations and tissue eosinophil counts (> 10/HPF). Weak to moderate correlations were also found between the type 2 inflammatory markers such as the serum ECP concentration, blood eosinophil count, and serum total IgE, and tissue eosinophil count (data not shown). Taken together, the determination of residual sinus inflammation may be based on both the severity of type 2 eosinophilic inflammation and extent of the inflammation involved.[39] The serum ECP concentration and tissue eosinophil count can only reflect the degree of type 2 eosinophilic inflammation.[12] Thus a comprehensive evaluation of the severity and extent of type 2 eosinophilic inflammation in CRSwNP is necessary to predict the therapeutic outcomes after sinus surgery and the need for post-op adjuvant therapy such as biologic therapy.[45]

Owing to the lack of a single ideal predictor including comorbid asthma, NPS, LMS, E/M ration, and olfactory cleft opacification score in the ROC analysis, we propose a nomogram to predict the probability of post-op residual sinus inflammation in patients with eosinophilic CRSwNP by simultaneously evaluating five clinical variables based on regression analysis results. The total points obtained by calculating the sum of the corresponding scores from these variables provide better precision in predicting the risk of post-op residual sinus inflammation in each patient with eosinophilic CRSwNP. This could help clinicians better evaluate therapeutic outcomes of surgery in patients with eosinophilic CRSwNP and may provide additional adjuvant therapy to facilitate the recovery of post-op sinonasal residual inflammation.

This study had several limitations. First, only patients who underwent sinus surgery in as single centre were enrolled. Patients with milder disease or those who were unwilling to undergo surgery were not recruited and selection bias may have occurred. Nevertheless, all patients diagnosed with bilateral CRSwNP who underwent sinus surgery during the study period were eligible and included to minimise selection bias. Second, this study was conducted in a tertiary referral medical centre and the disease severity of CRSwNP may have been higher than that of the general population. High NPS, LMS, and symptom scores were observed in participants of the current study. However, these patients have the greatest potential to be refractory to surgery and may require adjuvant therapy such as biologics, which warrants further investigation. Third, half of our participants did not undergo the olfaction test because of the COVID-19 pandemic. Instead, we determined the olfactory cleft opacification score using CT images to evaluate the inflammation severity in the olfactory mucosa of patients with eosinophilic CRSwNP. Fourth, we did not determine whether these clinical markers could predict long-term treatment response in the current study. Furthermore, limitations of the use of nomogram by the moderate predictive power and lack of external validation should be acknowledged. All these highlighting the need for future reports with large scale and long-term post-op outcomes. However, our findings emphasise that the detection of post-op residual sinus inflammation may be based on both the severity of type 2 eosinophilic inflammation and the extent of sinonasal inflammation. Thus, a comprehensive evaluation of the severity and extent of type 2 eosinophilic inflammation in patients with CRSwNP is necessary to predict the surgical outcomes and the need for post-op adjuvant therapy.

Conclusion

The determination of post-op residual sinus inflammation may be based on both the severity of type 2 eosinophilic inflammation and the extent of the sinonasal inflammation. Comorbid asthma, NPS, LMS, E/M ratio, and olfactory cleft opacification score were significant predictors of post-op residual sinus inflammation in patients with eosinophilic CRSwNP. This can help clinicians to better evaluate therapeutic outcomes after sinus surgery and predict the need for post-op adjuvant therapy such as biologics.

Abbreviations

CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyp; IL, interleukin; ECP, eosinophil cationic protein; ESS, Endoscopic sinus surgery; post-op, postoperative; IgE, immunoglobulin E; SNOT-22, sinonasal outcome test- 22; CT, computed tomography; NPS, nasal polyp score; MLK score, modified Lund-Kennedy endoscopic score; HPF, high power field; LMS, Lund-Mackay score; E/M ratio, ethmoid/maxillary ratio; ROC curve, receiver operating characteristic curve; AUC, area under the curve; NSAID, non-steroidal anti-inflammatory drugs - exacerbated respiratory disease; WBC, white blood cell; BEC, blood eosinophil count; TEC, tissue eosinophil count.

Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author, [Chein-Chia H.].

Author Contributions

Chien-Chia H: Conceptualization, Data curation, Formal analysis, Funding acquisition and Writing – review and editing; PWW: Data curation, Formal analysis and Writing – original draft. PHC: Data curation and Supervision; Chi-Che H: Data curation and Supervision; YHF: Formal analysis and Visualization; CIY: Data curation. All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest.

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