

Systemic Predictors of Eosinophilic Chronic Rhinosinusitis

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Abstract

Background: Eosinophilic chronic rhinosinusitis (eCRS) is linked with skewed T-helper 2 or immunoglobulin E (IgE)-mediated allergic responses, with differing diagnosis, prognosis, and management to non-eCRS.

Objective: The association between biomarkers and eCRS was investigated to assess the predictors of eCRS.

Methods: A cross-sectional study of adult patients with chronic rhinosinusitis (CRS) undergoing endoscopic sinus surgery was conducted. eCRS was defined by histopathological assessment showing >10 eosinophils/high-power field on sinus mucosal biopsy. Blood tests were performed preoperatively and assessed for a full blood count including eosinophils and a white cell count (WCC) as well as biochemical markers of inflammation and atopy including Immunoglobulin E (IgE), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and ImmunoCAP testing for serum-specific IgE. Comparisons between eCRS and non-eCRS patients were performed.

Results: 345 patients (48.1% female, age 48.72 ± 15.06 years) were recruited, with 206 (59.7%) identified as eCRS, 41% with asthma and 47% CRS with nasal polyps. eCRS patients were more likely to have asthma ($P < .01$) and nasal polyps ($P < .01$). Blood eosinophils were significantly elevated in eCRS (0.42 ± 0.34 vs $0.17 \pm 0.13 \times 10^9/L$, $P < .01$) as were eosinophils as a ratio of WCC (6.21 ± 4.48 vs 2.55 ± 1.84 , $P < .01$). ESR was decreased when compared with non-eCRS (8.1 ± 7.87 vs 10.65 ± 11.91 , $P = .03$). Receiver operating characteristic curve analysis predicted high tissue eosinophilia at blood eosinophil levels above $0.24 \times 10^9/L$ (sensitivity 70.9%, specificity 78.4%, area under the curve [AUC]: 0.792, $P < .01$). eCRS was predicted at eosinophil above 4.27% of total WCC (sensitivity 64.1%, specificity 88.5%, AUC 0.797; $P < .01$; positive predictive value 89.2%, negative predictive value 62.4%, positive likelihood ratio 5.57, and diagnostic odds ratio 13.71). There was no significant association among WCC, CRP, IgE, or ImmunoCAP testing.

Conclusion: eCRS is associated with elevated blood eosinophils ($>0.24 \times 10^9/L$), eosinophil ratio ($>4.27\%$ of total WCC), and lower ESR when compared with non-eCRS.

Keywords

chronic rhinosinusitis, eosinophilic chronic rhinosinusitis, eosinophils, biomarkers, atopy, blood tests, cross-sectional studies, diagnosis, human, adult

Introduction

Eosinophilic chronic rhinosinusitis (eCRS) is an emerging classification of chronic rhinosinusitis (CRS), which is thought to more accurately reflect the underlying pathophysiology. eCRS is thought to be a disease of chronic sinus inflammation rather than infection,

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linked with skewed T-helper 2 (TH2) allergic responses, driven by eosinophilic inflammation and a dysregulated sinus mucosa.¹ eCRS is diagnosed by the histopathological assessment of eosinophilic infiltration within sinus tissue. There is a wide variation within the literature, and no consensus currently exists regarding the cutoff for the diagnosis of eCRS; however, an absolute eosinophil count of >10 per high-power field (HPF) is generally associated with poorer outcomes and overall prognosis.²⁻⁴

Following from this, patients with eCRS have differing presentations, management, and prognosis to the non-eCRS subtype. Patients often present with symptoms of loss of smell, long-term nasal congestion, thick mucus production, and intermittent acute exacerbations due to secondary bacterial infections. eCRS is difficult to treat, often being refractory to medical and surgical interventions and associated with disease recurrence.⁵ Therefore, it would be useful to be able to identify these patients with eCRS early, preferably within the outpatient setting, in order to guide overall long-term management and prognosis.

Biomarkers are measurable objective indicators of a disease state and are utilized to diagnose, monitor, and assess the treatment response. It can be hypothesized that individual factors driving the local inflammatory process at the mucosal level may be identifiable in the systemic circulation. In CRS with nasal polyps (CRSwNP), peripheral eosinophilia has been linked with increased infiltrating eosinophil counts as well as increased type 2 innate lymphoid cells within nasal polyps.^{6,7} The aim of this study was to assess the association between blood markers and tissue eosinophilia and to identify the potential predictors of eCRS.

Methods

Study Design

A cross-sectional study of patients undergoing functional endoscopic sinus surgery (FESS) at Macquarie University and St Vincent's Hospital was performed. This study had ethical approval from the St Vincent's Hospital Human Research Ethics Committee (SVH 09/083), and patients provided informed consent for research data collection.

Patient Population

Adult patients (≥ 18 years) diagnosed with CRS, according to the European Position Paper on Rhinosinusitis and Nasal Polyps⁸ and undergoing FESS as part of the management for their disease, seen at a tertiary referral clinic over a 6-year period (May 2010 to May 2016) were included.

Patients with established immunodeficiency, coagulation disorder, pregnancy, classic allergic fungal sinusitis, recent oral corticosteroid use, or cystic fibrosis were excluded from the study.

Demographic characteristics were recorded including patient's age, gender, asthma, and previous surgery. Asthma status was determined by either a 15% change in forced expiratory volume in 1 second on spirometry result on challenge testing or β -agonist use, or if currently using regular inhaled bronchodilator or corticosteroid therapy. Previous CRS surgery was defined as any previous procedure as surgical intervention for CRS and thus now undergoing a revision operation.

Presence of polyps was assessed from nasal endoscopy images performed on the first clinic visit. Patients with nasal polyps of greater than grade 1, according to the Lund-Mackay grading system,⁹ were determined to have nasal polyps.

All patients had ceased systemic corticosteroid medication for at least 4 weeks prior to their surgery.

Determination of eCRS

Sinus mucosal specimens were obtained intraoperatively and placed in formalin. These were then processed with standard hematoxylin and eosin staining and assessed by pathologists blinded to the clinical data. eCRS was defined by histopathological assessment showing >10 eosinophils/HPF (400 $\times$ magnification) on two separate HPFs.^{2,4}

Blood Parameters

A blood sample was taken at the time of surgery and assessed for a number of potential markers including eosinophils, white cell count (WCC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), total immunoglobulin E (IgE), and ImmunoCAP test for detecting specific IgE antibodies to common aeroallergens (grass mix, house dust mite mix, animal epithelia mix, mold mix). Positive atopy status was defined as either elevated total IgE (>160 kU/L) or any positive ImmunoCAP test for allergen-specific IgE (>0.35 kU/L). Eosinophil ratio was calculated by dividing the eosinophil count by the WCC and expressed as a percentage. All parameters were assessed in a blinded fashion.

Statistical Analysis

Comparisons between eCRS and non-eCRS patients were performed. Statistical analysis was performed using SPSS Statistics v22 (SPSS, Inc., Chicago, IL). Parametric results are expressed as mean $\pm$ 1 standard deviation.

Independent samples *t*-test was utilized for continuous data and χ^2 test for proportional data. Receiver operating characteristic (ROC) analysis was utilized to determine

the optimal cutoff for the prediction of a diagnosis of eCRS, and the area under the curve (AUC) was calculated. All *P* values are 2-tailed and a value of *P* < .05 was considered statistically significant.

Results

A total of 345 patients (48.1% female, age 48.72 ± 15.06 years) were recruited, with 206 (59.7%) classified as eCRS; 46.7% had CRSwNP, 40.6% had asthma, 50.4% had undergone previous surgery for CRS, and 61.2% were classed as atopic.

A comparison between eCRS and non-eCRS characteristics is presented in Table 1. There were no significant differences among age, gender, or previous CRS surgery between the eCRS and non-eCRS groups. Patients diagnosed with eCRS were more likely to have asthma ($\chi^2(1)=29.76$, *P* < .01) and nasal polyps ($\chi^2(1)=120.38$, *P* < .01), reflecting the TH2 inflammatory nature of the disease.

Biomarkers

A comparison of biomarkers between eCRS and non-eCRS is summarized in Table 2.

Blood Eosinophils. Eosinophils were significantly elevated in eCRS population compared with the non-eCRS group ($0.42 \pm 0.34 \times 10^9/L$ vs $0.17 \pm 0.13 \times 10^9/L$; *P* < .01). ROC curve analysis predicted high tissue eosinophilia (>10/HPF) at cutoff level $0.24 \times 10^9/L$ (sensitivity 70.9%, specificity 78.4%, AUC: 0.792, *P* < .01) (Figure 1). This cutoff level produced a positive predictive value (PPV) of 83.0%, negative predictive value (NPV) of 64.5%, positive likelihood ratio (LR+) of 3.28, and diagnostic odds ratio (DOR) of 8.84.

Eosinophils: WCC Ratio. Furthermore, when eosinophils were assessed as a percentage of the total WCC, this was significantly elevated in eCRS population (6.21 ± 4.48 vs 2.55 ± 1.84 , *P* < .01). ROC curve analysis

Table 1. Comparison of eCRS and Non-eCRS Characteristics.

	eCRS (n=206)	Non-eCRS (n=139)	<i>P</i>
Age (years)	48.45 ± 14.34	49.12 ± 16.11	.68
Female (%)	45.1	52.5	.18
Nasal polyps (%)	70.9	10.8	<.01**
Asthma (%)	52.4	23.0	<.01**
Previous CRS surgery (%)	52.4	47.5	.37

Abbreviations: CRS, chronic rhinosinusitis; eCRS, eosinophilic chronic rhinosinusitis.

**Indicates significant results

predicted eCRS at a cutoff level of 4.27% (sensitivity of 64.1%, specificity of 88.5%, AUC 0.797; *P* < .01) (Figure 2). This result yielded a PPV 89.2%, NPV 62.4%, LR+ 5.57, and DOR 13.71.

Acute Phase Reactants. Acute phase proteins such as WCC, CRP, and ESR represent nonspecific systemic markers of inflammation used generally in medicine for the diagnosis and monitoring of the progress of the disease.¹⁰ WCC was decreased when compared with the

Table 2. Comparison of Biomarkers Between eCRS and Non-eCRS Populations.

Patients	eCRS (n=206)	Non-eCRS (n=139)	<i>P</i>
Eosinophils ($\times 10^9/L$)	0.42 ± 0.34	0.17 ± 0.13	<.01**
WCC ($\times 10^9/L$)	6.94 ± 2.08	7.47 ± 2.73	.052
Eosinophil/WCC ratio (%)	6.21 ± 4.48	2.55 ± 1.84	<.01**
CRP (mg/L)	2.41 ± 3.93	3.18 ± 4.70	.11
ESR (mm/h)	8.10 ± 7.87	10.65 ± 11.91	.03**
IgE (kU/L)	182.31 ± 293.93	146.64 ± 280.72	.26
Overall ImmunoCAP +ve (%)	51.9	48.2	.50
Grass mix (%)	35.0	28.1	.19
House dust mite mix (%)	32.0	30.9	.86
Animal epithelia (%)	13.6	12.2	.73
Mold mix (%)	16.0	10.1	.13

Abbreviations: CRP, C-reactive protein; eCRS, eosinophilic chronic rhinosinusitis; ESR, erythrocyte sedimentation rate; IgE, immunoglobulin E; WCC, white cell count.

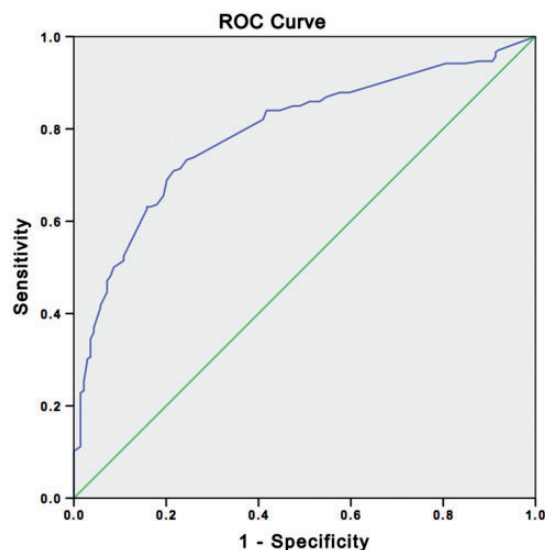


Figure 1. Receiver operating characteristic (ROC) curve of blood eosinophils to predict tissue eosinophil ≥ 10 /high-power field.

non-eCRS population; however, this was not statistically significant (6.94 ± 2.08 vs 7.47 ± 2.73 ; $P = .052$). There was no significant association between tissue eosinophilia and CRP (2.41 ± 3.93 vs 3.18 ± 4.70 , $P = .11$). ESR was decreased in the eCRS population when compared with non-eCRS (8.10 ± 7.87 vs 10.65 ± 11.91 , $P = .03$).

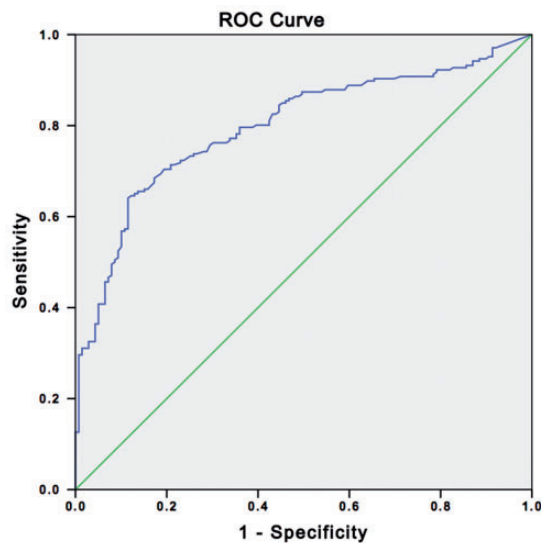


Figure 2: Receiver operating characteristic (ROC) curve of blood eosinophil: white cell count ratio to predict tissue eosinophil ≥ 10 /high-power field.

Further analysis with ROC curve showed nonsignificant findings (AUC 0.456, $P = .17$).

Allergic Markers. An IgE-driven inflammatory process has been hypothesized to contribute to the pathophysiology of both CRS and eCRS.¹¹ There was no significant association between tissue eosinophilia and overall positive allergen-specific IgE ($\chi^2(1) = 0.464$, $P = .50$), nor with any particular allergen-specific IgE (grass, house dust mite, animal epithelia, or mold mix) (Table 2). While there was a higher mean serum total IgE level shown in the eCRS population, this was not statistically significant (182.31 ± 293.93 vs 146.64 ± 280.72 , $P = .26$).

Discussion

eCRS is associated with treatment failure, recurrence of nasal polyps, and poorer quality of life. In this study, we investigated a number of biomarkers and their potential role in identifying eCRS.

Studies evaluating the association between blood and tissue eosinophilia in eCRS are summarized in Table 3. There is no agreed upon definition for the tissue classification of eCRS, with significant variation within the identified studies as well as in the general literature.¹⁶

This study showed an ideal blood eosinophil count cutoff of $0.24 \times 10^9/L$ to predict eCRS with moderate specificity (78.4%), PPV (83.0%), and DOR (8.84). However, it has low sensitivity (70.9%), NPV (64.5%),

Table 3. Summary of Studies Investigating Association Between Blood Eosinophilia and eCRS.

Reference	Year	n	Definition of eCRS	Association
This study	2018	345 CRS (206 eCRS, 139 non-eCRS)	$>10/HPF$	Blood eosinophil predicted eCRS at $>0.235 \times 10^9/L$ (sensitivity 70.9%, specificity 78.4%; AUC: 0.792) Eosinophil/WCC ratio predicted eCRS at $>4.265\%$ with sensitivity 64.1% and specificity 88.5% (AUC: 0.797)
Gitomer et al. ¹²	2016	70 CRSwNP (56 eCRS, 14 non-eCRS)	$>10/HPF$	No relationship between blood eosinophilia and tissue eosinophilia (AUC 0.59, $P = .40$)
Zuo et al. ¹³	2014	105 CRS (73 eCRS, 32 non-eCRS)	$>5/HPF$	Blood eosinophil predicted eCRS at $>0.16 \times 10^9/L$ with sensitivity 84.9% and specificity 84.4% (AUC: 0.873) Eosinophil/WCC ratio predicted eCRS at $>2.05\%$ with sensitivity 89.0% and specificity 84.4% (AUC: 0.863)
Snidvongs et al. ²	2012	49 CRS (23 eCRS, 26 non-eCRS)	$>10/HPF$	Blood eosinophil predicted eCRS at $>0.30 \times 10^9/L$ and 4.4% WCC (sensitivity 52%, specificity 87%)
Hu et al. ¹⁴	2012	155 CRSwNP (66 eCRS, 89 non-eCRS)	% tissue eosinophils $>10\%$ total infiltrating cells	Blood eosinophil predicted eCRS at $>0.215 \times 10^9/L$ (sensitivity 74.2%, specificity 86.5%; AUC: 0.871) Eosinophil/WCC ratio predicted eCRS at $>3.05\%$ (sensitivity 80.3%, specificity 75.3%; AUC 0.864)
Sakuma et al. ¹⁵	2011	124 CRSwNP (39 eCRS, 85 non-eCRS)	Clinical diagnosis + CT imaging	Eosinophil/WCC ratio predicted eCRS at $\geq 6\%$ WCC (sensitivity 97.4%, specificity 70.7%)

Abbreviations: AUC, area under the curve; CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyps; CT, computed topography; eCRS, eosinophilic chronic rhinosinusitis; HPF, high-power field microscopy.

and LR+ (3.28). Overall, the results show that while there is an association, its utility as a surrogate marker for tissue eosinophilia remains limited. This may be related to the eosinophil itself, as circulating eosinophil counts can be falsely elevated by comorbid parasite infection, allergy, autoimmune disorders, or adverse drug events.¹⁷ In addition, local eosinophil actions at the tissue level such as activation and migration often occur without elevation of blood eosinophils.¹⁸

Blood eosinophils have previously been shown to have moderate diagnostic accuracy in detecting eosinophilic asthma, acting as a surrogate marker for sputum eosinophilia.¹⁹ Mepolizumab is an anti-IL-5 monoclonal antibody that is currently used for the management of severe eosinophilic asthma and has been acclaimed as a potential treatment in the management of eCRS. The standard cutoff applied for Australian government subsidized provision of mepolizumab for eosinophilic asthma is a blood eosinophil count of $0.3 \times 10^9/L$. When applying this cutoff to the population within this study, this yielded a sensitivity of 62.6% and a specificity of 84.2%. A lower blood eosinophil level ($>0.24 \times 10^9/L$) may be more appropriate in the setting of other clinical features of eCRS as a marker for eosinophilic inflammation.

However, eosinophil to WCC ratio also represented a specific measure for eCRS in this study. We found that a ratio of 4.27% had a significant specificity of 88.5% and sensitivity of 64.1%. There was a significant PPV (89.2%), LR+ (5.57), and DOR (13.71), reflective of a useful biomarker for eCRS. This is consistent with previous studies showing an association between eosinophil percentage and eCRS and represents the largest population studied to date. With further investigation, this may prove a useful marker for the initiation of biological therapies as well as directing the length and intensity of corticosteroid treatment.

Sakuma et al. classified patients as eCRS based on clinical diagnostic criteria of clinical features, CT scan findings, peripheral blood eosinophil count above normal range, and postoperative clinical course.¹⁵ As these eCRS patients were already defined by elevated eosinophil count, the resultant eosinophil percentage cutoff may be falsely elevated and potentially omit patients with tissue confirmed eCRS. On the other hand, Gitomer et al. showed no relationship between blood and tissue eosinophilia in CRSwNP patients; however, as a case series with chart review, they were unable to control for possible oral steroid use prior to tissue sampling. In addition, 21.4% of patients within the study were identified as having concurrent oral steroid use, which may adversely affect blood eosinophil count and thus overall association.¹² Within these identified studies, there is also a wide variation in the proposed cutoff levels, and importantly, these blood eosinophil counts are all within the normal laboratory

reference range (generally $0-0.4 \times 10^9/L$), making it difficult to distinguish from low eosinophil counts of non-eCRS. It is notable that in our ROC analysis, the cutoff blood eosinophil count was below the upper limit of the reference range.

Interestingly, this study showed that ESR was significantly elevated in non-eCRS when compared with eCRS. As a nonspecific marker of inflammation, ESR has been previously implicated in acute rhinosinusitis with levels of >30 and >40 resulting in LR+ of 4.08 and 7.40, respectively, which is, however, not routinely recommended for the diagnosis.²⁰ The mean ESR level for non-eCRS in this study was 10.71 mm/h which is only slightly higher than the reference range 0 to 10 mm/h, and there was a substantial overlap between the eCRS and non-eCRS and thus ESR presents as a poor option as a biomarker for non-eCRS.

WCC and CRP, other systemic markers of inflammation, showed no significant difference with eCRS subgroups with the overall mean WCC and CRP in this study in the reference range ($<11 \times 10^9/L$ and <5 mg/L, respectively). CRP has been previously shown to have no significant elevation between CRS phenotypes and controls.²¹ Markers of atopy such as total IgE and allergen-specific IgE based on ImmunoCAP testing were not associated with tissue eosinophilia, which may reflect eCRS as a disease driven by a TH2 response dominated by eosinophilia rather than IgE. The evidence for anti-IgE therapies such as omalizumab in CRS remains insufficient and is the subject of further investigation.²² Furthermore, the role of atopy in CRS is controversial with mixed data regarding its association.²³ Huang et al. have previously shown no significant differences in peripheral eosinophil counts between groups compared based on presence of polyps and atopic factors.²⁴

The data shown in this study represent a large cohort assessing the relationship between routine CRS workup blood tests and the diagnosis of eCRS. However, these were not evaluated in conjunction with clinical features or imaging, as is done in the routine outpatient practice when diagnosing patients. A future direction of this research will be to investigate predictive modeling combining clinical features, imaging, and blood tests to identify patients with eCRS.

Conclusion

eCRS is associated with elevated blood eosinophils ($>0.24 \times 10^9/L$), eosinophil ratio ($>4.27\%$ of total WCC), and lower ESR when compared with non-eCRS. Tissue analysis remains the gold standard for the diagnosis of eCRS; however, blood eosinophil percentage may represent a useful indicator for eCRS.

Authors' Note

This paper was presented at the 4th South Pacific Otorhinolaryngology Forum on 12th July 2017.

Ethics

Ethical approval was obtained from the St Vincent's Hospital Human Research Ethics Committee (SVH 09/083).

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Richard J Harvey is a consultant with Medtronic, Olympus and NeilMed pharmaceuticals. He has also been on the speakers' bureau for Glaxo-Smith-Kline, Seqiris and Astra-Zeneca. All other authors have no conflicts of interest.

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