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Profile of Tissue Immunoglobulin E in Eosinophilic Chronic Rhinosinusitis with Nasal Polyps

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Keywords
Chronic rhinosinusitis · Immunoglobulin E · Allergic rhinitis · Eosinophil · Nasal polyps

Abstract
Introduction: Eosinophilic chronic rhinosinusitis with nasal polyps (eCRSwNP) exhibits a poorer prognosis than noneCRSwNP. The aim of this study was to analyze the potential of total immunoglobulin E (tIgE) and specific IgE (sIgE) levels in tissues for distinguishing and assessing eCRSwNP. ***Methods:*** We enrolled 10 control and 88 CRSwNP patients. The clinical data of patients were collected before surgery. Nasal mucosa tissues were taken during surgery for measurements of tIgE, sIgE (weed pollen, epidermal and animal protein, mold, house dust, tree pollen), and subepithelial eosinophil (EOS) counts. The predictive significance of the potential predictors for eCRSwNP was assessed with receiver operating characteristic (ROC) curves. ***Results:*** Nasal polyps tIgE and mold-sIgE were positively correlated with blood and tissue EOSs, comorbid allergic rhinitis and asthma, ethmoid score/total maxillary score ratio, visual analog scale, and CT score. The ROC curve analysis showed that tissue tIgE ($p = 0.0004$), mold-sIgE ($p = 0.0030$), blood EOS percentage ($p = 0.0003$), and absolute blood EOS count ($p = 0.0010$) acted as predictive factors for eCRSwNP. According to the cutoff value of tissue tIgE of 34.55 ku/L, patients with a high level were more likely to suffer from asthma ($p = 0.016$) and showed a significantly higher EOS count ($p = 0.022$), EOS percentage ($p = 0.029$), and tIgE ($p = 0.002$) in blood. ***Conclusion:*** Tissue tIgE and mold-sIgE had a significant relationship with the clinical and pathological characteristics of CRSwNP patients and might be reliable for distinguishing and assessing eCRSwNP.

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Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is considered to be a heterogeneous disease, and patients often present with symptoms such as nasal congestion, nasal discharge, reduction in smell, and facial pain [1]. Eosinophilic chronic rhinosinusitis with nasal polyps (eCRSwNP, as opposed to the noneCRSwNP subtype) is linked to dysregulated T-helper 2 (Th2) allergic inflammation responses and is often refractory to medical and surgical interventions. eCRSwNP responds well to oral

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glucocorticoids [2] but always has a high risk of relapse after surgery [3], while noneCRSwNP responds well to postoperative macrolide therapy [4].

There was significant variation upon definition for the classification of eCRSwNP. Currently, several clinical characteristics, such as eosinophils (EOSs) in tissue [3, 5], blood [6], and nasal fluids [7], and the ethmoid score/total maxillary score (E/M ratio) [8], are used to identify eCRSwNP. However, the diagnosis of eCRSwNP as an absolute EOS count of >10/high-power field (HPF) was supported by the European position paper on rhinosinusitis and nasal polyps from 2020 (EPOS2020). Th2 CRS also tends to be characterized by a blood EOS count ≥0.25 $\times 10^9$/L or total immunoglobulin *E* (tIgE) ≥100 kU/L [1]. Snidvongs et al. [9] suggested that the clinical use of blood EOSs was limited. Distinguishing eCRSwNP from noneCRSwNP, based on the pathogenic mechanism, provided a more precise picture, appropriate for use in guiding postoperative medication and reducing recurrence [10, 11].

In Th2 inflammation, plasma cells secrete immunoglobulin E (IgE), which acts on mast cells and basophils. Allergen challenge across the nasal mucosa results in crosslinking of IgE bound to mast cells and basophils with degranulation, leading to the recruitment of other inflammatory cells. Fungal IgE, which is highly detectable in NP tissues but not in blood, has greater effects on local inflammation in CRSwNP patients with asthma than in those without asthma [12, 13]. In approximately one-quarter of CRSwNP patients, IgE to staphylococci was correlated with concomitant asthma [14] and recurrence after surgical or systemic glucocorticoid treatment [15]. With the increasing recognition of the role of Th2 immune responses in chronic rhinosinusitis and their severity, recurrence, and comorbidities, biologically targeted IgE has been administered in several high-quality studies [16, 17]. Thus, the tIgE or specific IgE (sIgE) level might be a reliable biomarker for predicting a diagnosis of eCRSwNP. In this study, we analyzed the relationship of tIgE and common sIgE in NP tissues with the clinical and pathological characteristics of CRSwNP patients to highlight their distinguishing and assessing values for eCRSwNP and their use in guiding postoperative medication.

Materials and Methods

Patients

A total of 88 consecutive patients with CRSwNP and 10 controls from 2010 to 2021 were enrolled in Peking Union Medical College Hospital (PUMCH). The diagnosis of CRSwNP was made according to the EPOS2020 guidelines. Patients with deviated nasal septum who did not present with sinusitis were enrolled as the control group. The protocol of the present study was approved by the Ethics Committee of PUMCH, and written informed consent was obtained from all patients. No patient was treated with antibiotics and/or topical or systemic corticosteroids for at least 1 month before the operation. Allergic rhinitis (AR) and asthma were diagnosed on the basis of medical history and results of physical examination. Fungal sinusitis, cystic fibrosis, antrochoanal polyps, immunodeficiency, or sinonasal tumors were excluded. Concomitant asthma was diagnosed by pneumologists based on the history and pulmonary function test.

Overall subjective symptoms, including nasal obstruction, nasal discharge, reduction or loss of smell, and facial pain, were evaluated using a visual analog scale (VAS). The complete peripheral blood cell count and differential white blood cell counts were measured with an automatic hemocyte analyzer. Blood tIgE levels were detected by means of the ImmunoCAP system (Thermo Fisher Scientific, Waltham, MA, USA). All patients underwent CT, and the Lund-Mackay scoring system was used to evaluate the preoperative CT score, the E/M ratio of CT was calculated.

Analyses of Local IgE

Nasal polyp tissues were weighed and homogenized on ice with a power homogenizer (KZ-II, Wuhan, China). One milliliter of phosphate-buffered saline and 10 μL of protease inhibitors (Thermo Fisher Scientific, Waltham, MA, USA) were added to every 100 mg of tissue. The suspensions were centrifuged at 10,000 rpm for 10 min at 4°C. The IgE levels were detected by the ImmunoCAP system as described above. sIgE was determined for weed pollen mix (wx5, common ragweed, mugwort, marguerite, dandelion, and goldenrod), epidermal and animal protein mix (ex1, dander from cat, horse, cow, and dog), mold mix (mx2, *Penicillium notatum*, *Cladosporium herbarum*, *Aspergillus fumigatus*, *Candida albicans*, and *Alternaria*), house dust mix (hx2, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, and *Blatella germanica*), and tree pollen mix (tx5, gray alder, hazel, Elm, Willow, and cottonwood).

Hematoxylin and Eosin Staining

Sinus mucosal specimens were obtained intraoperatively and placed in formalin and then processed by means of standard hematoxylin and eosin staining. Tissue EOSs and differential white blood cells in an HPF were counted in a blinded manner by two observers. The EOS ratio was calculated by dividing the EOS count by the subepithelial granulocyte count and expressed as a percentage.

Statistics

SPSS, version 22.0 (SPSS, Chicago, IL, USA) was used to perform data analysis. Continuous variable differences were analyzed by Student's *t* test or Mann-Whitney U test. Sex, smoking, asthma, and AR were compared using the χ^2 test. Pearson correlation coefficients were calculated to assess the associations between biomarkers. Receiver operating characteristic (ROC) curves were used to evaluate the prediction ability for eCRSwNP, and the best cutoff value was determined with the Youden index. p value <0.05 was considered significant.

Table 1. Clinical characteristics

	Control	noneCRSwNP (EOS < 10)	eCRSwNP (EOS ≥ 10)	*p* value
Gender (M/F)	4/6	21/2	46/19	0.047*
Age	41.9±15.4	42.2±17.2	49.6±13.6	0.067
History, year	0	9.0±11.5	9.4±8.3	0.909
Smoking	2/10	7/23	22/65	0.765
AR	0	15/23	46/65	0.620
Asthma	0	10/23	28/65	0.134
Blood EOS, %	1.1±0.8	4.0±3.7	7.7±4.6	0.001*
Blood EOS	0.07±0.04	0.29±0.29	0.53±0.35	0.011*
VAS score	NA	29±7	30±6	0.689
CT score	0	17±5	19±4	0.043*
E/M ratio	0	2.3±0.7	2.5±0.8	0.254
ImmunoCAP tests				
Blood tIgE	NA	174.2±193.9	162.0±195.6	0.824
Tissue tIgE	6.15±5.0	25.9±24.7	71.8±79.0	0.006*
Specific IgE				
wx5	0.06±0.01	0.13±0.11	0.18±0.09	0.157
ex1	0.08±0.02	0.18±0.10	0.35±0.23	0.113
mx2	0.08±0.02	0.15±0.08	0.25±0.14	0.003*
hx2	0.09±0.03	0.17±0.15	0.26±0.19	0.337
tx5	0.04±0.01	0.10±0.08	0.16±0.10	0.020*

NA, not available; CRSwNP, chronic rhinosinusitis with nasal polyps; EOS, eosinophil; IgE, immunoglobulin E; wx5, weed pollens mix; ex1, epidermals and animal protein; mx2, mold mix; hx2, house dust mix; tx5, tree pollens mix; VAS, visual analog scale; E/M ratio, ethmoid score/total maxillary score; Mean ± SD; *p* value represents the difference between eCRSwNP and noneCRSwNP. * $p < 0.05$.

Results

Subject Characteristics

A total of 88 patients with CRSwNP and 10 controls were enrolled in this study. CRSwNP patients had higher EOSs in blood than control patients ($p < 0.0001$). According to the absolute EOS count of ≥10/HPF, NPs were divided into 65 cases of eCRSwNP and 23 cases of noneCRSwNP. Compared with noneCRSwNP patients, eCRSwNP patients demonstrated higher blood EOSs, local tIgE ($p = 0.006$), mx2-sIgE ($p = 0.003$), and higher CT scores ($p = 0.043$) (Table 1).

Associations between Local tIgE Level and Clinical Characteristics

In peripheral blood, the EOS ratio and absolute value had a strong correlation ($p < 0.0001$). Absolute blood EOS count was also correlated with tissue EOS ($p = 0.042$) and tissue tIgE ($p = 0.038$) (online supplementary Fig. S1; see www.karger.com/doi/10.1159/000522624 for all online suppl. material). The higher the tIgE level in NP tissues was, the higher the EOSs and tIgE levels in blood (Fig. 1a, d). There were significant differences in tissue tIgE levels between patients with and without AR or asthma. Tissue tIgE was correlated with VAS score ($p = 0.007$), CT score ($p = 0.013$), and E/M ratio ($p = 0.005$) (Fig. 1f–i). There were no differences in blood tIgE between patients with and without AR ($p = 0.092$) or asthma ($p = 0.109$). Blood tIgE was also not correlated with CT score ($p = 0.095$), E/M ratio ($p = 0.892$), or VAS score ($p = 0.857$). Taken together, the tIgE level in NP tissues, not in blood, had a strong correlation with local and systemic factors in our CRSwNP patient cohort.

Associations between Local sIgE Level and Clinical Characteristics

CRSwNP patients had higher tIgE, mx2-sIgE, and tx5-sIgE levels in tissues than control patients ($p < 0.01$). In local tissues, all five kinds of detectable sIgE for inhaled allergens were positively correlated with tIgE ($p < 0.0001$). Through the analysis of five kinds of detectable sIgE in local tissues, the level of mx2-sIgE had positive associations with blood and tissue EOSs, VAS scores, E/M ratio, CT scores, and comorbid AR and asthma (Table 2; Fig. 1j, k).

Table 2. The association between clinical characteristics and detectable sIgE in nasal polyps

	wx5		ex1		mx2		hx2		tx5	
	r	*p* value	*r*	*p* value	*r*	*p* value	*r*	*p* value	*r*	*p* value
Blood tIgE	0.071	0.504	0.232	0.028*	0.217	0.038*	0.126	0.236	0.194	0.067
Tissue tIgE	0.623	<0.0001*	0.835	<0.0001*	0.463	<0.0001*	0.659	<0.0001*	0.58	<0.0001*
Blood EOS,%	0.124	0.215	0.178	0.073	0.254	0.010*	0.065	0.542	0.132	0.187
Blood EOS	0.112	0.261	0.133	0.181	0.306	0.002*	0.086	0.392	0.119	0.232
Tissue EOS,%	0.102	0.344	0.200	0.062	0.230	0.031*	0.112	0.299	0.152	0.156
Tissue EOS	0.103	0.341	0.066	0.542	0.233	0.029*	0.012	0.911	0.188	0.079
VAS score	0.098	0.327	0.186	0.062	0.287	0.003*	0.104	0.298	0.225	0.023*
CT score	0.124	0.213	0.156	0.118	0.341	0.000*	0.094	0.347	0.277	0.005*
E/M ratio	0.209	0.035*	0.095	0.343	0.287	0.003*	0.043	0.669	0.268	0.006*

EOS, eosinophil; IgE, immunoglobulin E; wx5, weed pollens mix; ex1, epidermals and animal protein; mx2, mold mix; hx2, house dust mix; tx5, tree pollens mix; VAS, visual analog scale; E/M ratio, ethmoid score/total maxillary score. *r* was calculated by pearson correlation. * $p < 0.05$.

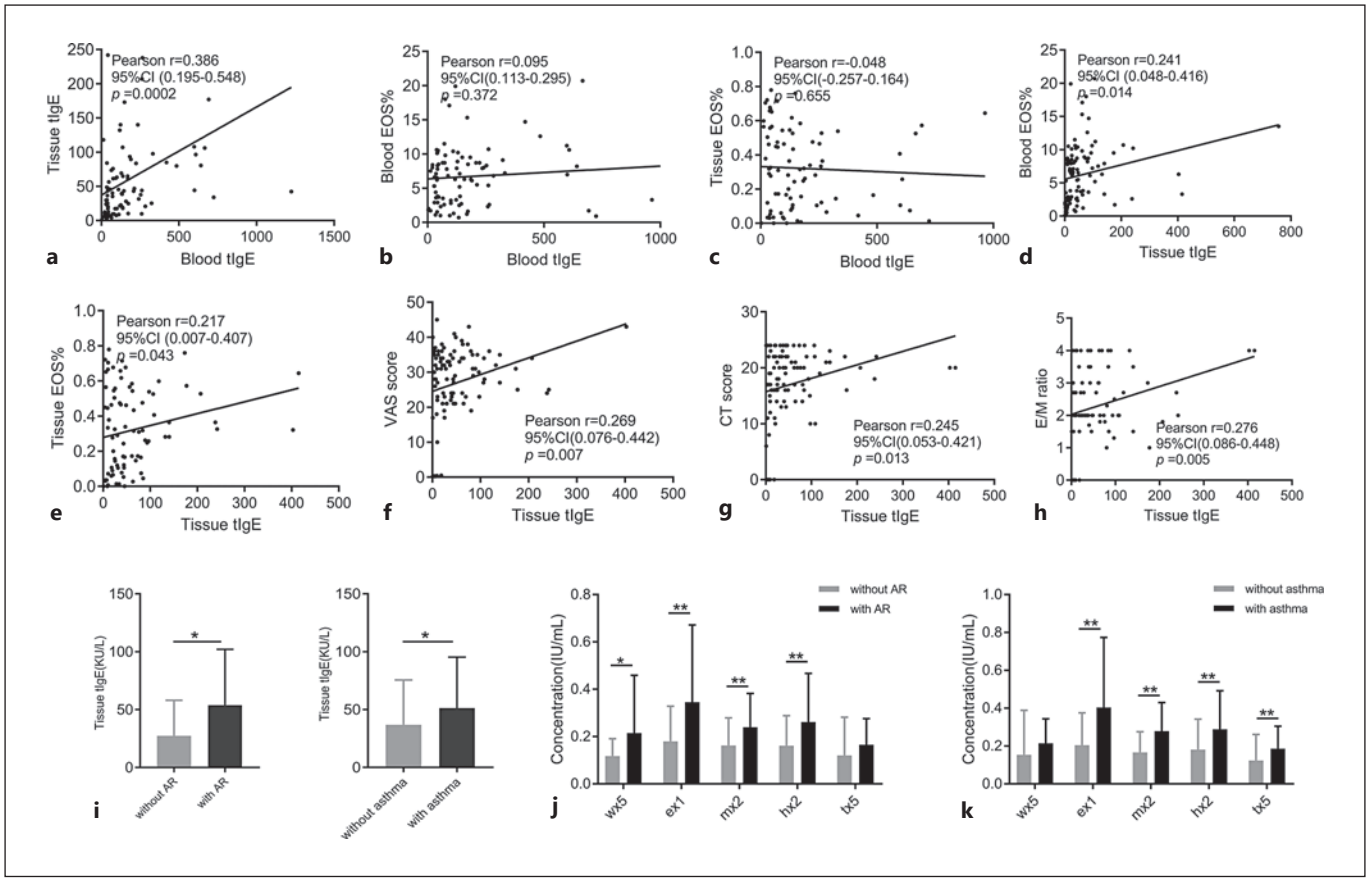


Fig. 1. The correlation between IgE in blood and tissues and clinical characteristics. **a–e** The correlation between EOS and tIgE in blood and tissues. tIgE in blood and EOS ratio (**a**); tIgE in blood and EOS ratio (**b**, **c**); tIgE in tissues and EOS ratio (**d**, **e**). The correlation between tIgE in tissues and VAS score (**f**), CT score (**g**), E/M ratio (**h**), comorbid AR and asthma (**i**). The difference in sIgE between CRSwNP with and without AR (**j**), asthma (**k**). *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. EOS, eosinophil; IgE, immunoglobulin E; AR, allergic rhinitis; 95% CI, 95% confidence interval;.

Table 3. Area under the ROC curves, sensitivity, and specificity at the cutoff value

Predictors	AUC (95% CI)	Cutoff value	Sensitivity	Specificity	*p* value
Blood EOS,%	0.755 (0.629–0.882)	3.25	86.2	65.2	0.0003
Blood EOS	0.730 (0.594–0.866)	0.175	89.2	56.5	0.0010
Tissue tIgE	0.750 (0.640–0.860)	34.55	66.2	73.9	0.0004
mx2-sIgE	0.709 (0.586–0.832)	0.105	92.3	43.5	0.0030
Blood tIgE	0.523 (0.390–0.658)	–	–	–	0.7308

EOS, eosinophil; IgE, immunoglobulin E; AUC, area under the curve; CI, confidence interval; IgE, immunoglobulin E; mx2, mold mix.

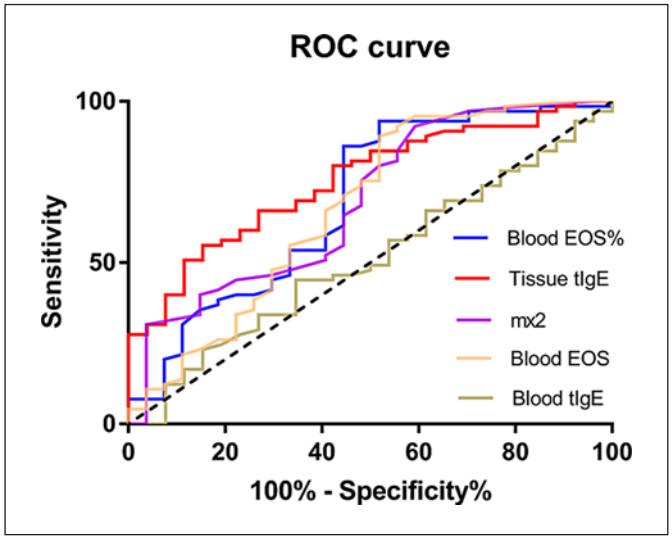


Fig. 2. ROC curves to predict eCRSwNP for variables based on a tissue EOS cutoff value. IgE, immunoglobulin E; EOS, eosinophil.

Table 4. Comparison of clinical characteristics between the high and the low tIgE level group

	CRSwNP		*p* value
	tIgE (–)	tIgE (+)	
Gender (M/F)	19/2	29/13	0.060
Age, years	46.7±17.5	47.2±14.2	0.238
History, years	9.4±11.7	9.2±8.3	0.821
Smoking	7/21	13/42	0.848
AR	12/21	39/42	0.257
Asthma	5/21	21/42	0.016*
Blood EOS, %	3.9±3.0	7.7±4.8	0.029*
Blood EOS	0.24±0.19	0.55±0.36	0.022*
VAS score	30±6	30±6	0.372
CT score	17±5	19±4	0.048*
E/M ratio	2.3±0.7	2.5±0.8	0.088
Histopathological findings (H&E staining)			
Tissue EOS, %	0.23±0.27	0.35±0.22	0.092
Tissue EOS	41.0±41.3	57.6±48.2	0.041*
ImmunoCAP tests			
Blood tIgE	79.2±77.7	209.9±218.8	0.002*
sIgE			
wx5	0.09±0.24	0.21±0.10	0.110
ex1	0.11±0.05	0.37±0.21	0.005*
mx2	0.11±0.04	0.27±0.12	0.000*
hx2	0.17±0.04	0.30±0.20	0.047*
tx5	0.07±0.02	0.18±0.10	0.000*

CRSwNP, chronic rhinosinusitis with nasal polyps; EOS, eosinophil; IgE, immunoglobulin E; wx5, weed pollens mix; ex1, epidermals and animal protein; mx2, mold mix; hx2, house dust mix; tx5, tree pollens mix; VAS, visual analog scale; E/M ratio, ethmoid score/total maxillary score. Mean ± SD. * $p < 0.05$.

Assessment of the Diagnostic Value of Tissue IgE for eCRSwNP

Patients were classified as either eCRSwNP ($n = 65$) or noneCRSwNP ($n = 23$) based on a tissue EOS absolute count of ≥10 or <10/HPF of the total infiltrating cells, respectively. The ROC curves of the biomarkers for distinguishing eCRSwNP from noneCRSwNP are shown in Figure 2. The area under the curve and 95% confidence interval (CI) of the parameters blood EOS percentage, absolute blood EOS count, tissue tIgE, mx2-sIgE, and blood tIgE (Table 3) were 0.755 (95% CI = 0.629–0.882), 0.730(95% CI = 0.594–0.866), 0.750 (95% CI = 0.640–0.860), 0.709 (95% CI = 0.586–0.832), and 0.523 (95% CI = 0.390–0.658), respectively. However, the *p* value of the ROC curve for blood tIgE was 0.7308. The cutoff value of the blood EOS percentage in tissues was 3.25% (sensitivity 86.2%, specificity 65.2%). The cutoff value of absolute blood EOS count was 0.175 × 10^9/L (sensitivity 89.2%, specificity 56.5%). The optimal cutoff value of tissue tIgE was 34.55 kU/L (sensitivity 66.2%, specificity 73.9%).

Based on the cutoff value of tissue tIgE, patients with a high level were more likely to suffer from asthma ($p = 0.016$) and showed a significantly higher EOS count ($p =$

0.022), EOS percentage ($p = 0.029$), and tIgE ($p = 0.002$) in blood. Moreover, in patients with high tIgE levels, CT scores ($p = 0.048$) were significantly higher than those with low levels (Table 4).

Discussion

eCRSwNP is associated with more frequent comorbid asthma and AR, higher CT scores, and higher blood EOS counts than noneCRSwNP [8, 18, 19]. The association between the presence of specific inflammatory cells (especially EOSs) and the prognosis and recurrence of CRSwNP, has been reported [20]. These studies lack comparisons between EOSs in tissues and peripheral blood. Local EOS activation and migration in the tissue often occur without elevations in blood EOSs. In view of the important role of Th2 inflammation mediated by EOSs in the pathogenesis of nasal polyps, distinguishing eCRSwNP from noneCRSwNP is crucial for personalized medicine to minimize the side effects of medical therapy before or after surgery and the recurrence rate of nasal polyps.

EOSs could be defined using a cutoff value based on reference values from healthy mucosa, but typical disease-specific values should also be employed to increase sensitivity and specificity for clinical use [21]. Our study demonstrated an association between tIgE and EOSs in tissues. Blood EOS count and percentage were correlated with tIgE in nasal polyps, but not in peripheral blood. Moreover, tIgE in nasal polyps was significantly correlated with tIgE levels in blood ($p = 0.0002$) and the clinical characteristics of patients, such as comorbid asthma and AR, CT score, E/M ratio, and VAS score. In CRSwNP, tIgE in the nasal mucosa correlated significantly with the local ECP [13]. Indeed, ROC curve analysis suggested that tissue tIgE, mold-sIgE, blood EOS count, and percentage had a high accuracy in predicting eCRSwNP.

Our study also demonstrated a significant association between mold-sIgE and EOSs in local tissue. The levels of mold-sIgE were positively correlated with comorbid asthma and AR, CT score, VAS score, and E/M ratio in CRSwNP patients. This was in accordance with the findings of Ohki et al. [12], who showed that a higher prevalence of asthma and increased CT scores were frequently linked to fungal sIgE in local tissue in both allergic fungal sinusitis and CRSwNP patients. Exposure to *Alternaria* was a risk factor for respiratory arrest in patients with asthma [22] and induced Th2 cytokine production in the human airway epithelium, the initial interface with airborne allergen [23]. Thus, immune responses to environmental mold might increase the production of cytokines and provide cellular activation signals, including IgE synthesis, that lead to eosinophilic inflammation in patients. Therefore, mold-sIgE might play an important role in CRSwNP pathogenesis by inducing Th2 immune responses.

Current knowledge indicates that the pathology of eCRSwNP is associated not only with Th2-IgE but also with ILC2-driven IgE-independent mechanisms. ILC2s, lack of antigen recognition receptors, provide the primary innate cellular source of the type 2 cytokines that drive eosinophilic inflammation [24]. Human ILC2s can express CD154 and release IL-4/IL-13, thus stimulating the production of IgE by B cells. Not only ILC2 but also circulating Th2 cell numbers did not correlate with serum IgE levels [25]. For patients with AR, IgE was produced locally in the nasal mucosa instead of inflammatory cells in peripheral blood. In the nasal mucosa exposed to air allergens, the number of IgE-positive B and plasma cells increased significantly [26]. eCRSwNP is highly correlated with AR, and a high local expression of IgE often indicates more severe Th2 allergic inflammatory responses [27].

CRSwNP patients treated with Dupilumab (anti-IL-4/13) [28] or Omalizumab (anti-IgE) [17] therapy had significant improvement in the Sino-Nasal Outcome Test-22, rhinosinusitis disease severity, nasal blockage, smell score, nasal polyp score, and CT score compared to placebo. Although Dupilumab is the only monoclonal antibody that is approved for the treatment of CRSwNP [29], anti-IgE treatment has become a critical part of alleviating the atopic state and recurrence of nasal polyps in clinical work [16]. The dosage of biologically targeted IgE is often based on IgE in serum. Clinical testing of IgE is limited to free IgE in serum, which ignored the cell-bound IgE, and this may be the reason why serum IgE levels in some allergic patients are normal. Therefore, the detection of serum IgE concentration cannot accurately reflect the level of systemic IgE. In fact, the ROC curve analysis in our study suggested that tIgE in serum (area under the curve = 0.523) did not seem to have assessing value for eCRSwNP. Understanding the content of tIgE in tissues early as soon as possible is of great significance for anti-IgE treatment.

In our studies, the levels of tIgE in NPs were correlated with the presence of five kinds of detectable sIgE. Matsuwaki et al. [13] demonstrated that mite sIgE in the sinus mucosa correlated significantly with EOSs in NP tissues, which was different from our results. It seemed that mite

sIgE did not have a significant association with markers of the severity of CRSwNP, such as CT score, VAS score, and E/M ratio. In contrast, we found that the level of spring tree pollen sIgE was positively correlated with the above markers. This might be related to the fact that most of the cases we enrolled in the group were collected in spring and summer. However, little is known about house dust mites or spring tree pollen allergens among Chinese CRSwNP patients, and this needs more cases and further exploration.

There were some limitations in our studies. Our research did not involve the value of serum-sIgE, and to some extent, some data would be lost, and the correlation between serum and tissue IgE could not be accurately determined; however, this aspect was not the focus of this study. Indeed, for patients who are managed conservatively or unwilling to undergo a biopsy, we cannot accurately determine the IgE in their nasal mucosal tissue. In future, we hope to find factors that are strongly related to nasal mucosal IgE, which can be obtained in noninvasive samples. Our study was limited to a single medical center in Beijing. We should conduct a nationwide multicenter study to validate the results in other cohorts, which needs to be further investigated in the future.

Conclusion

Local tissue IgE, especially mold-sIgE, was correlated with EOSs in tissues and blood, VAS and CT scores, and the E/M ratio. Compared with tIgE in blood, local tissue tIgE seemed to have assessing value for eCRSwNP to minimize the side effects of medical therapy before or after surgery and the recurrence rate of nasal polyps. Overall, these findings suggested that tissue IgE might be a reliable biomarker for distinguishing and assessing eCRSwNP and was important in guiding anti-IgE treatment strategies, pending confirmation from other studies with a higher level of complexity.

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Statement of Ethics

The human participants provided written consent to participate in the study. This study protocol was reviewed and approved by the Ethics Committee of Peking Union Medical College Hospital, approval number JS-2620.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

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Author Contributions

J.H., W.W., Z.Z., L.W., Y.C., and W.L.: provided interpretation of data and critical feedback, and gave final approval for submission. R.W. and K.G.: performed statistical analyses, provided interpretation of data and critical feedback, and gave final approval for submission. W.L.: acquired data, contributed to the conception and design of the study, provided interpretation of data and critical feedback, and gave final approval for submission.

Data Availability Statement

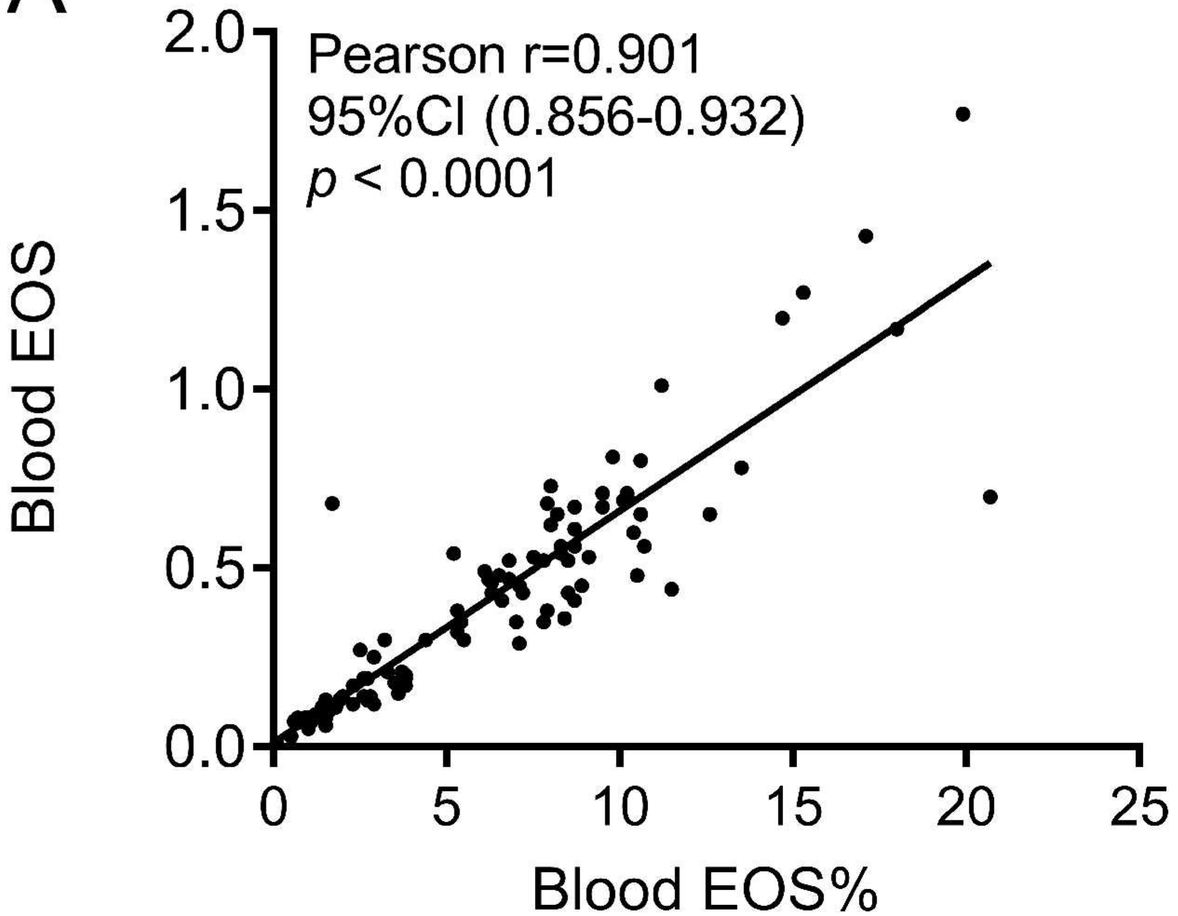
The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author upon reasonable request.

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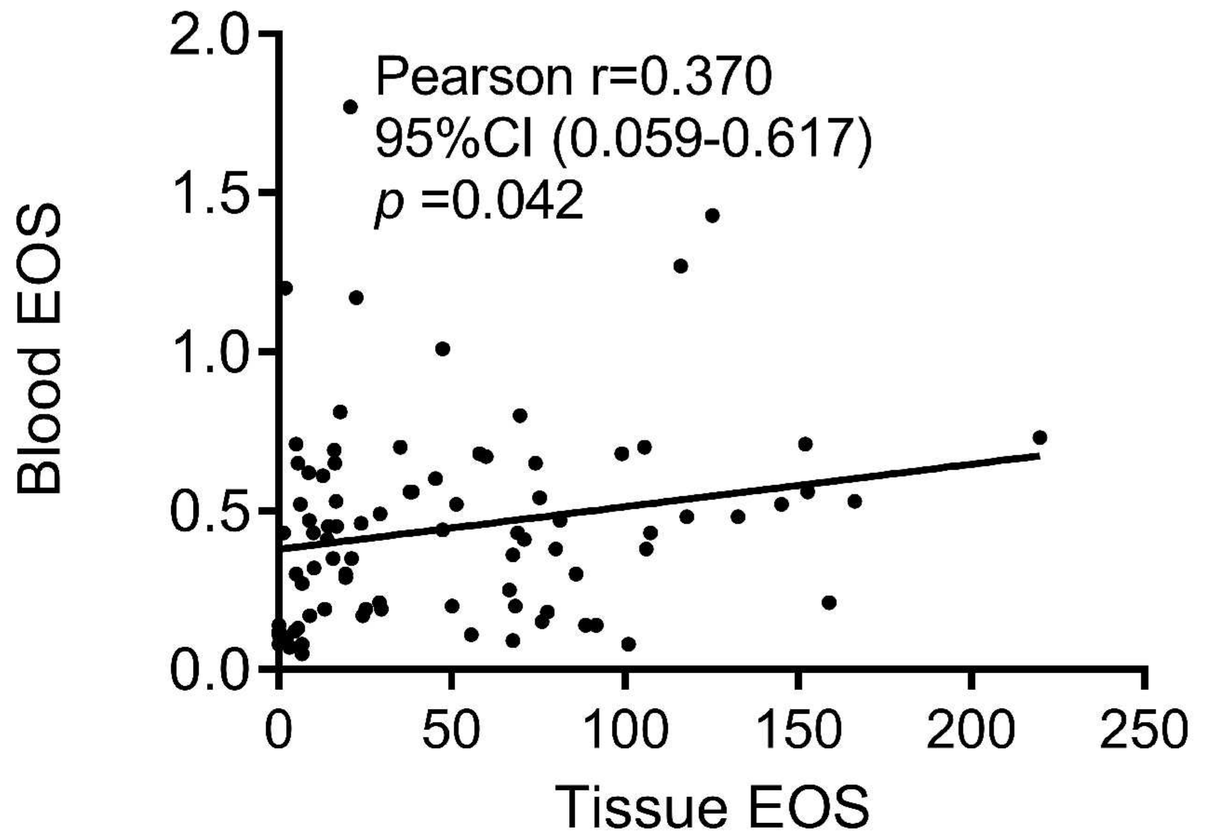
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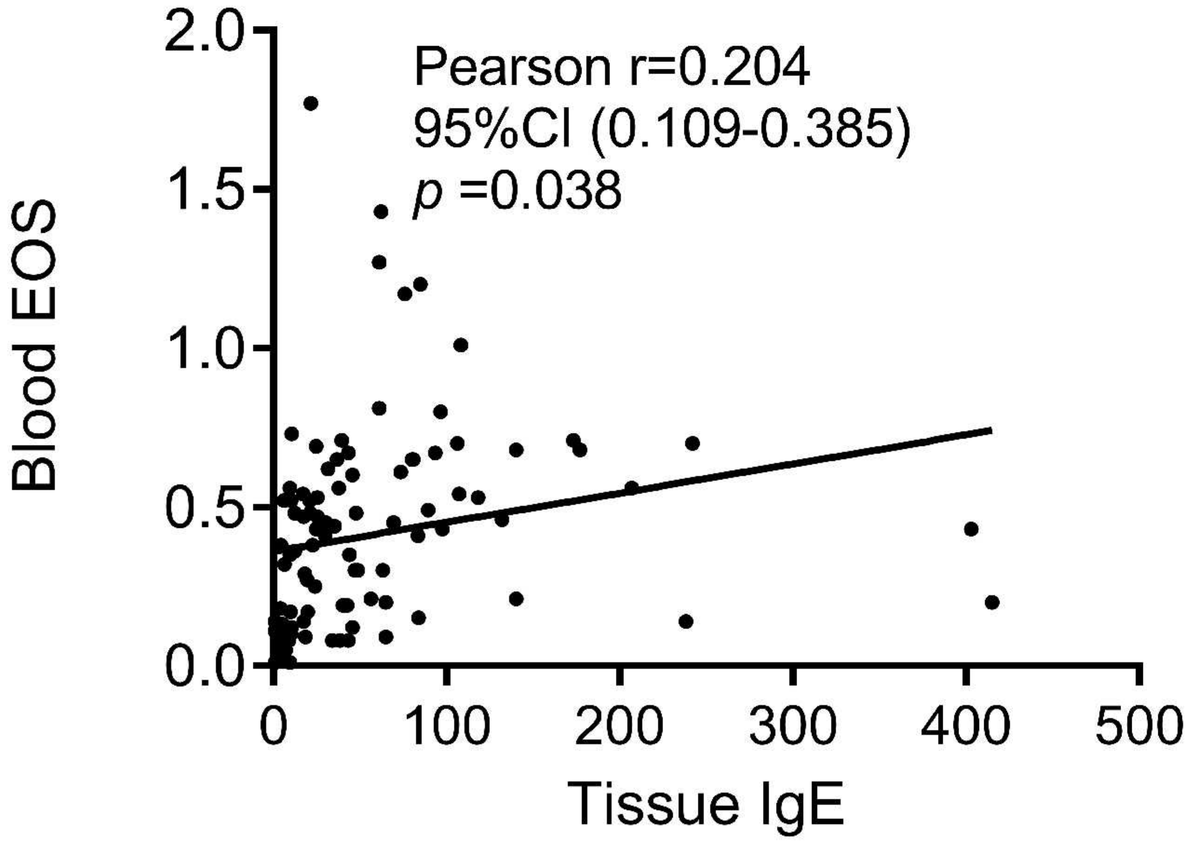
A


Pearson r=0.901
95%CI (0.856-0.932)
p < 0.0001
Blood EOS
Blood EOS%
0.0
0.5
1.0
1.5
2.0
0
5
10
15
20
25

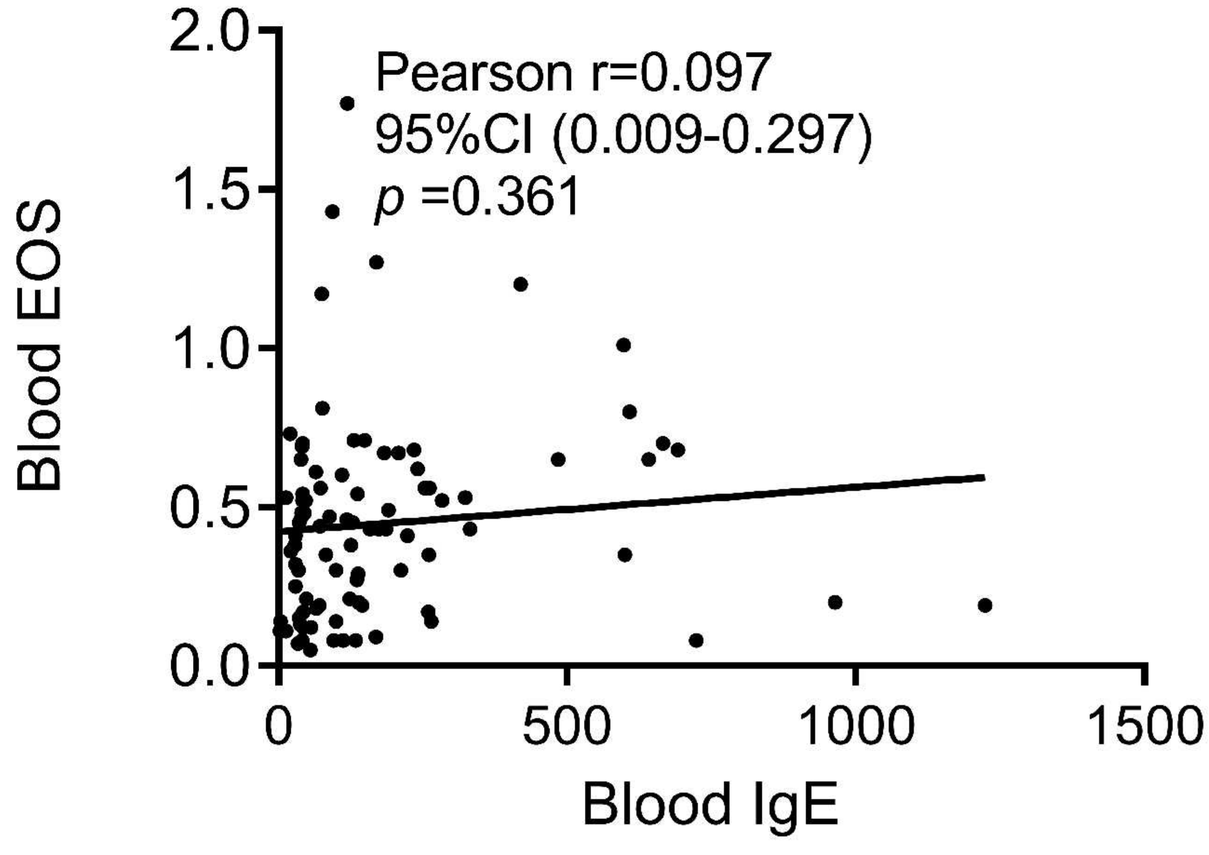
B


Pearson r=0.370
95%CI (0.059-0.617)
p =0.042
Blood EOS
Tissue EOS
0.0
0.5
1.0
1.5
2.0
0
50
100
150
200
250

C


Pearson r=0.204
95%CI (0.109-0.385)
p =0.038
Blood EOS
Tissue IgE
0.0
0.5
1.0
1.5
2.0
0
100
200
300
400
500

D


Pearson r=0.097
95%CI (0.009-0.297)
p =0.361
Blood EOS
Blood IgE
0.0
0.5
1.0
1.5
2.0
0
500
1000
1500