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ORIGINAL RESEARCH

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Clinical characteristics of patients with CRSwNP with intensely high eosinophil level

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Abstract

Background: High tissue and blood eosinophils are linked to poor treatment outcome in patients with chronic rhinosinusitis with nasal polyps (CRSwNP). However, the difference between the patients with different level of blood or tissue eosinophilia in relation to disease control is still lacking.

Objectives: This study aimed to characterize patients with CRSwNP with intensely high eosinophil level.

Methods: A retrospective study of CRSwNP patients underwent endoscopic sinus surgery was conducted. The patients were subdivided with various cut-off values of blood and tissue eosinophils. Tissue eosinophils of ≥50% and 10%–20% were defined as intensely high tissue eosinophils (IH-tissue-eos) and high tissue eosinophils (H-tissue-eos), respectively. Blood eosinophils of $\geq 0.6 \times 10^9$/L and 0.2×10^9/L–0.3×10^9/L were defined as intensely high blood eosinophils (IH-blood-eos) and high blood eosinophils (H-blood-eos). Clinical characteristics, Lund-Mackay score (LMS), and disease control status were compared between subgroups.

Results: A total of 302 patients were enrolled. There was a trend toward a higher rate of uncontrolled disease when the patients subdivided by blood eosinophil cut-off values ranged from 0.1×10^9/L to 0.6×10^9/L. The controlled patients accounted for 27%, 36%, 22%, and 31%, and the uncontrolled patients 46%, 32%, 52%, and 31% of patients in IH-tissue-eos, H-tissue-eos, IH-blood-eos, and H-blood-eos subgroup, respectively. The percentages of patients in the three categories of control were not significantly different between IH-tissue-eos and H-tissue-eos subgroups. By contrast, the IH-blood-eos subgroup had higher percentages of current smoker and asthma, preoperative LMS and tissue eosinophil percentage, and showed a trend toward a higher rate of uncontrolled subjects compare with the H-blood-eos subgroup.

Conclusion: CRSwNP patients with IH-blood-eos ($\geq 0.6 \times 10^9$/L) may be possibly associated with a poorer disease control than those with levels near the threshold of

Ling Ma, Jianbo Shi, and Kanghua Wang contributed equally to this work.

blood eosinophilia (0.2×10^9/L–0.3×10^9/L). Further larger, preferably prospective studies are needed to confirm this relationship.
Level of Evidence: 4.

KEYWORDS
disease control, eosinophil, nasal polyp, rhinosinusitis

1 | INTRODUCTION

Chronic rhinosinusitis (CRS) is a significant multifactorial inflammatory disease of the mucosa of the nasal cavity and paranasal sinuses and estimated to affect 5%–12% of the general population around the world: 8% in China, 12% in the USA, and 7%–27% in Europe.[1–3] CRS is usually divided into two phenotypes: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) based on the presence or absence of the formation of nasal polyps.[1,4] CRSwNP patients have more severity of clinical manifestation, impairment of quality of life and economic burden for individual and society compared to CRSsNP patients, making CRSwNP research more clinically important to clinicians and researchers.[5–7]

Type2 inflammation and eosinophil have been demonstrated to play an important role in the development of CRSwNP.[1,4,8,9] Recently, a consensus has been reached that CRSwNP can further be subdivided into eosinophilic (ECRSwNP) and noneosinophilic (non-ECRSwNP) CRSwNP according to the tissue eosinophil numbers.[1,4] ECRSwNP has been reported to be prevalent in western countries and mainly characterized by Th2-skewed responses. Furthermore, it is well-recognized that eosinophil inflammation is an important factor that associated with higher recurrence rates after endoscopic sinus surgery (ESS) and medication treatment in patients with CRSwNP.[10] Several studies also have revealed that peripheral blood eosinophil counts correlate to tissue eosinophil numbers in nasal polyps,[11–13] and peripheral blood eosinophil count was an important risk factor for uncontrolled CRS and nasal polyp recurrence.[14] Recently, we further showed that both local and systemic eosinophilia are independently associated to a poor treatment outcome after ESS in CRSwNP patients.[15,16] However, it is still unclear whether any significant clinical characteristics differ between patients with intensely high levels of tissue and blood eosinophil and those with levels near the threshold of tissue and blood eosinophilia. In this study, we performed a retrospective cohort study to characterize the patients with CRSwNP with intensely high eosinophil level.

2 | MATERIALS AND METHODS

2.1 | Subjects and clinical assessment

This study enrolled CRSwNP patients who were diagnosed with bilateral nasal polyps according to the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020[1] and had undergone ESS between January 2015 and December 2019 in the First Affiliated Hospital of Sun Yat-Sen University and the University of Hong Kong-Shenzhen Hospital. A total of 1181 Chinese patients with bilateral CRSwNP was initially identified. Then patients with the following items were excluded: (1) Patients were treated with systemic corticosteroids within 3 months or internasal corticosteroids within 1 month before surgery and routine blood test,[17] by cross-referencing patient's medication history with the electronic prescription record system. (2) Patients with fungal rhinosinusitis, cystic fibrosis, antrochoanal polyps, gastro-esophageal reflux disease, or sinonasal tumors. (3) Patients with a history of food allergies, allergic dermatitis, or helminth infection. (4) Patients were younger than 16 years. (5) Patients lack of the following information: sinus computed tomography, routine blood test before surgery, and tissue specimens. Preoperative data were collected, including gender, age, smoking habits, comorbidities (such as allergic rhinitis and asthma), prior sinus surgery history, preoperative blood eosinophil count, preoperative Lund-Mackay score (LMS) and ESS date. The length of medication treatment, mainly including intranasal and systemic corticosteroids and antibiotics needed to control disease, after ESS was collected from patients' medical record. The diagnosis of allergic rhinitis was based on the Allergic Rhinitis and its Impact on Asthma guideline.[18] The diagnosis of asthma was performed by a specialist physician and was established according to the Global Initiative for Asthma 2006 guideline.[19] LMS was performed based on review and scoring of computed tomography (CT) scan images by a trained researcher.[20]

A total of 452 patients were enrolled in the retrospective cohort study and followed up for the evaluation of treatment outcome. Clinical control status of CRSwNP was categorized as controlled, partly controlled, or uncontrolled, according to EPOS 2020.[1] Briefly, controlled CRSwNP is defined as presenting no bothersome symptoms (VAS score ≤5), with healthy, or almost healthy mucosa in the last month, and no need for systemic medicine to control the disease within the previous 6 months. Partly controlled patients experience fewer than two of the following: persistent nasal blockage; mucopurulent rhinorrhea/postnasal drip; facial pain; impaired smell; sleep disturbance/fatigue; diseased mucosa on endoscopy in the last month; and a need for rescue treatment within the previous 6 months. Uncontrolled CRS is defined as having ≥3 of the aforementioned features in the last month, despite rescue treatment.

Prior study demonstrated that the cutoff value of 10% tissue eosinophils among the total inflammatory cells was used to define Chinese patients with eosinophilic CRSwNP.[21] Thus, in this study, we defined high tissue eosinophils (H-tissue-eos) as those with tissue

eosinophils ranged from 10% to less than 20% which is near the threshold of disease diagnosis of eosinophilic CRSwNP. Additionally, another previous study for distinguishing eosinophilic and non-eosinophilic CRSwNP showed that an absolute blood eosinophil count of 0.215 × 10^9/L was defined as cutoff values in Chinese adults.[12] Beyond that, Wang et al reported increased blood eosinophil count (≥0.3 × 10^9/L) related independently to have uncontrolled disease in CRSwNP.[15] Thus, in this study, we defined high blood eosinophils (H-blood-eos) as those with an absolute blood eosinophil count of 0.2–0.3 × 10^9/L. We further defined the cutoff value of ≥50% for intensely high tissue eosinophils (IH-tissue-eos) and of ≥0.6 × 10^9/L for intensely high blood eosinophils (IH-blood-eos) because they each represented the top 10% of the total cohort.

Finally, a total of 302 patients with adequate preoperative clinical data and completed follow-up assessments after at least 1 year of ESS were included. Of note, data including some of the same CRSwNP subjects have been previously published by Wang et al.[15] The study flow chart is presented in Figure 1. All procedures performed in this study involving human participants were in accordance with the ethical standards of the first affiliated hospital of Sun Yat-sen University and the University of Hong Kong-Shenzhen Hospital research committee.

2.2 | Histopathologic assessment

Histopathologic analysis was performed as we previously described.[15] Briefly, nasal polyp tissues of all the enrolled CRSwNP patients were obtained during the surgery, fixed in 10% formalin, and embedded in paraffin. Specimens were cut into 4 μm sections, then stained with hematoxylin–eosin. The sections were observed under a microscope (Leica DM4 B; Leica, Wetzlar, Germany) in a blinded fashion regarding all clinical data by two independent observers. The top 5 densest, nonoverlapping cellular infiltrate fields of the subepithelial layer were chosen under low power field (100×) in each section.[22] Then eosinophil and total inflammatory cells were counted in the focus of each area under high power field (×400, 0.072 mm^2/frame, HPF). The ratio of eosinophils to total inflammatory cells was calculated.

2.3 | Statistical analysis

Statistical analyses were performed with SPSS version 23.0 statistical software (IBM SPSS, Armonk, NY). Continuous variables were presented as mean and standard deviation, categorical variables were presented as frequencies and percentage. *t*-tests were used for continuous variables with normal distribution. Mann–Whitney *U* tests were used for continuous non-normally distributed variables. χ^2 tests were used to evaluate differences in categorical variables, such as gender or smoking, allergic rhinitis prevalence. A logistic regression model with increased blood eosinophil count and increased tissue eosinophil percentage as independent predictors was performed to evaluate the treatment outcome. *p* value of less than .05 was considered statistically significant.

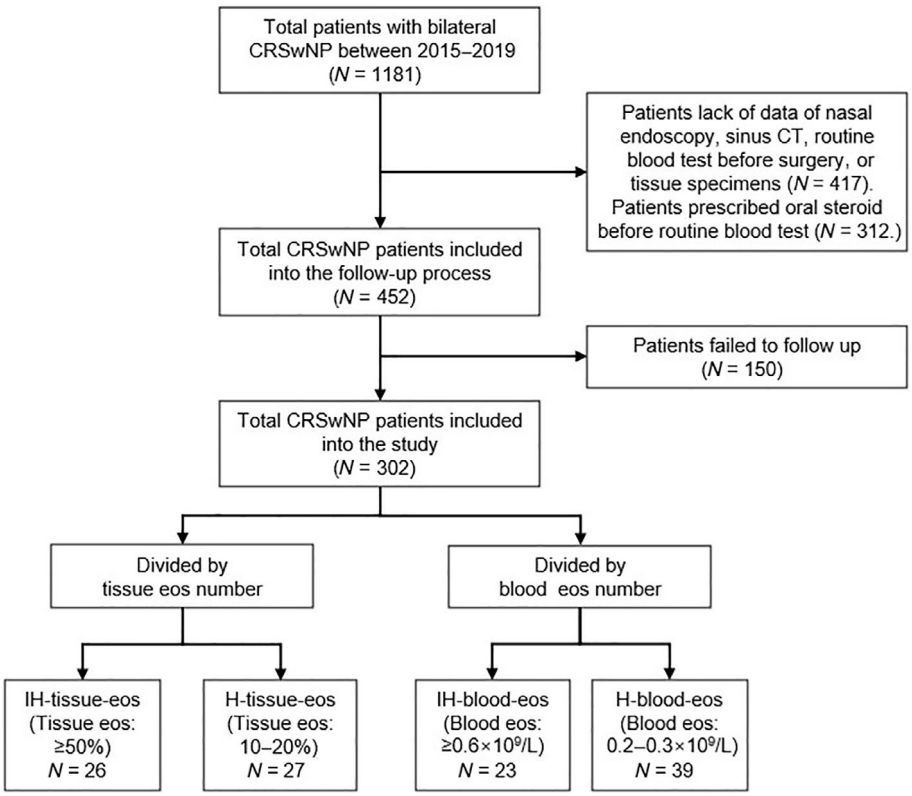

FIGURE 1 Flow diagram for patient enrollment, identification, and classification of the retrospective cohort. CRSwNP, Chronic rhinosinusitis with nasal polyps; Eos, eosinophil; H-tissue-eos, high tissue eosinophils; IH-tissue-eos, intensely high tissue eosinophils; H-blood-eos, high blood eosinophils; IH-blood-eos, intensely high blood eosinophils

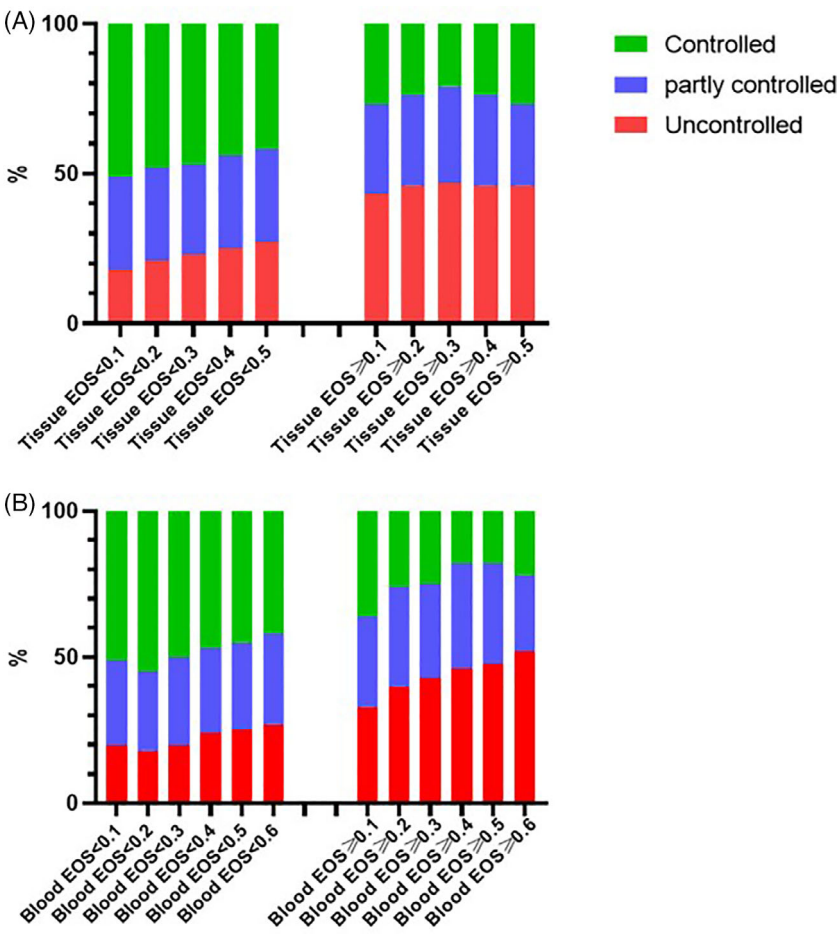

FIGURE 2 Trends in treatment outcomes among patients with CRSwNP by different tissue (A) and blood (B) eosinophil cut-off values. The percentages of treatment outcome in patients below (left side) and above (right side) various cut-off values for tissue and blood eosinophils were shown

TABLE 1 Characteristics between individuals with intensely high tissue eosinophils versus high tissue eosinophils

	IH-tissue-eos subgroup ($n = 37$)	H-tissue-eos subgroup ($n = 31$)	*p* value
Male, *n* (%)	26 (70.3%)	20 (64.5%)	.613
Age, mean (SD)	40.51 ± 11.51	43.45 ± 12.76	.708
Current smoker, *n* (%)	2 (5.6%)	4 (12.9%)	.534
Allergic rhinitis, *n* (%)	5 (13.5%)	7 (22.6%)	.329
Asthma, *n* (%)	11 (30.6%)	6 (19.4%)	.293
Preoperative L-M CT score, median (IQR)	19 (7)	15.5 (11.75)	.277
Blood eosinophil count, median (IQR) ($\times 10^9$/L)	0.38 (0.25)	0.26 (0.28)	**.021**
Blood eosinophil percentage, median (IQR)	0.058 (0.059)	0.044 (0.051)	.076
Tissue eosinophil count, median (IQR)	268 (220.13)	36 (42)	**<.001**
Tissue eosinophil percentage, median (IQR)	0.624 (0.112)	0.137 (0.05)	**<.001**
Medication length			.613
Medication length >6 months after surgery, *n* (%)	22 (59.5%)	16 (51.6%)	
Medication length 3–6 months after surgery, *n* (%)	8 (21.6%)	11 (35.5%)	
Medication length 1–3 months after surgery, *n* (%)	7 (18.9%)	4 (12.9%)	
Treatment outcome			.251
Controlled, *n* (%)	10 (27%)	11 (35.5%)	
Partly controlled, *n* (%)	10 (27%)	10 (32.3%)	
Uncontrolled, *n* (%)	17 (45.9%)	10 (32.3%)	

Abbreviations: CT, computed tomography; HPF, high power field; IQR, interquartile range; L-M, Lund-Mackay; H-tissue-eos, high tissue eosinophils; IH-tissue-eos, intensely high tissue eosinophils; SD, standard deviation.
Bold values highlight *P* value < 0.05.

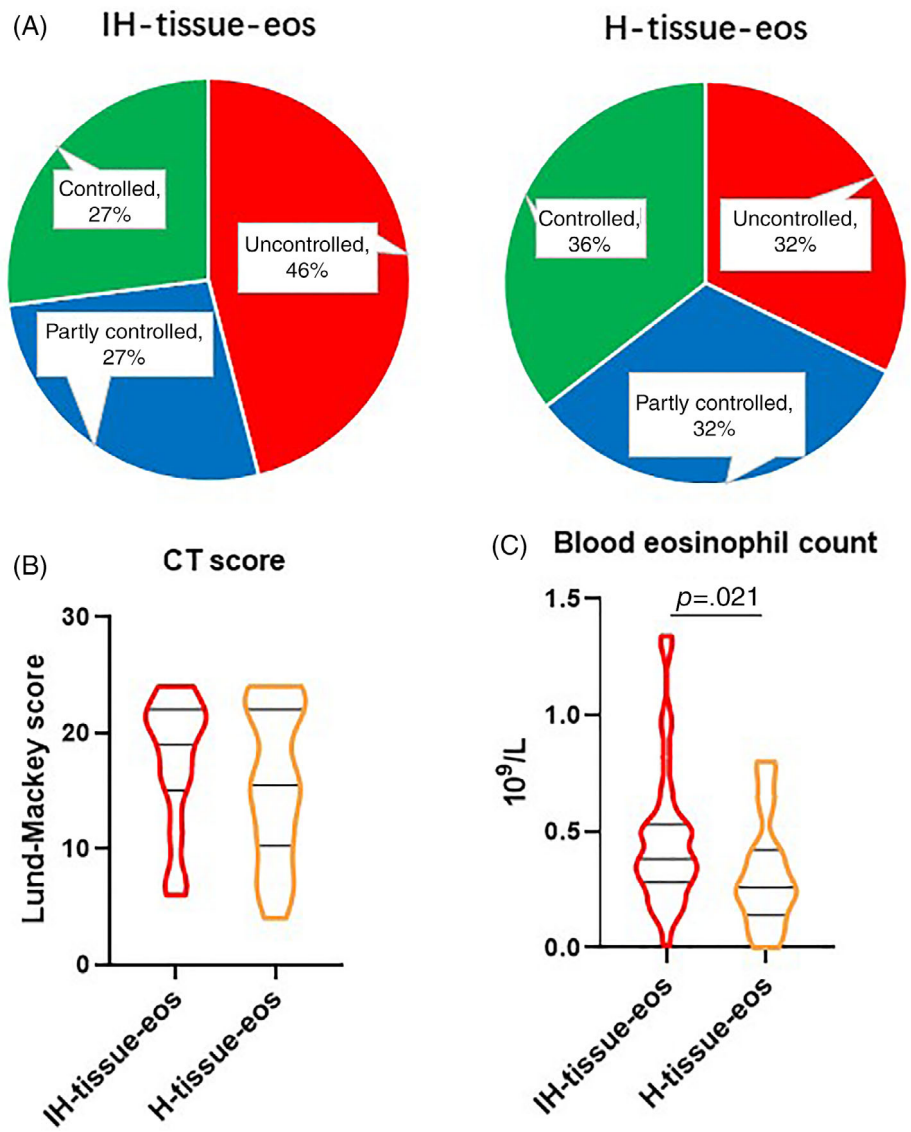

FIGURE 3 Prevalence of uncontrolled CRSwNP (A), CT score (B), and blood eosinophil count (C) in the subgroups with intensely high tissue eosinophils (IH-tissue-eos) and high tissue eosinophils (H-tissue-eos)

3 | RESULTS

3.1 | Baseline characteristics

The general characteristics of the cohort are presented in Table E1. Of 302 patients (202 males and 100 females) included for analysis, the average age was 41.26 ± 13.66 years. 28.5% of patients ($n = 86$) had a history of prior sinus surgery. About 8.3% of patients had known allergic rhinitis, 14.6% had asthma, 11.9% were current smokers, and 45.1% had postsurgery medication longer than 6 months. There were 40.1% of patients who had controlled disease, 30.8% with partly controlled disease, and 29.1% with uncontrolled disease.

3.2 | Treatment outcomes among patients with CRSwNP stratified by different tissue and blood eosinophil levels

We recently found that various tissue and blood eosinophil cutpoints were associated with an increased rate of uncontrolled disease in patients with CRSwNP.[15] In the present study, we further compared the treatment outcomes in the patients stratified by different tissue and blood eosinophil cut-off values. The results showed that the rate of uncontrolled disease was considerably stable when the patients stratified by tissue eosinophil cut-off values ranged from 10% to 50% (Figure 2A). By contrast, there was a trend toward a higher rate of uncontrolled disease but without statistical significance when the

TABLE 2 Characteristics between individuals with intensely high blood eosinophils versus high blood eosinophils

	IH-blood-eos subgroup ($n = 23$)	H-blood-eos subgroup ($n = 39$)	p value
Male, *n* (%)	17 (73.9%)	31 (79.5%)	.612
Age, mean (SD)	46.39 ± 11.82	40.00 ± 14.3	.076
Current smoker, *n* (%)	6 (26.1%)	2 (5.1%)	**.047**
Allergic rhinitis, *n* (%)	2 (8.7%)	1 (2.6%)	.635
Asthma, *n* (%)	9 (39.1%)	3 (7.7%)	**.007**
Preoperative L-M CT score, median (IQR)	20.5 (6.75)	14.87 (6.22)	**.01**
Blood eosinophil count, median (IQR) ($\times 10^9$/L)	0.77 (0.33)	0.23 (0.06)	**<.001**
Blood eosinophil percentage, median (IQR)	0.092 (0.065)	0.033 (0.018)	**<.001**
Tissue eosinophil count, median (IQR)	56.96 (113.53)	33 (61.45)	.341
Tissue eosinophil percentage, median (IQR)	0.241 (0.389)	0.114 (0.194)	**.044**
Medication length			.763
Medication length >6 months after surgery, *n* (%)	14 (60.9%)	25 (64.0%)	
Medication length 3–6 months after surgery, *n* (%)	6 (26.1%)	7 (17.9%)	
Medication length 1–3 months after surgery, *n* (%)	3 (13.0%)	7 (17.9%)	
Treatment outcome			.09
Controlled, *n* (%)	5 (21.7%)	12 (30.8%)	
Partly controlled, *n* (%)	6 (26.1%)	15 (38.5%)	
Uncontrolled, *n* (%)	12 (52.2%)	12 (30.8%)	

Abbreviations: CT, computed tomography; H-blood-eos, high blood eosinophils; HPF, high power field; IH-blood-eos, intensely high blood eosinophils; IQR, interquartile range; L-M, Lund-Mackay; SD, standard deviation.
Bold values highlight *P* value < 0.05.

patients subdivided by blood eosinophil cut-off values ranged from 0.1×10^9/L to 0.6×10^9/L (Figure 2B).

3.3 | Clinical characteristics of patients with intensely high eosinophil level

To further characterize the patients with intensely high eosinophil, we first compared the clinical characteristics between patients with IH-tissue-eos and those with H-tissue-eos (Figure 1). As a result, there were 37 patients with IH-tissue-eos and 31 patients with H-tissue-eos (Table 1). Both subgroups showed similar several clinical parameters, such as sex, age, percentages of current smoker, allergic rhinitis and asthma, preoperative Lund-Mackay CT score, and medication length after sinus surgery (Table 1, Figure 3B). As expected, the IH-tissue-eos subgroup had significantly higher blood eosinophil count than the H-tissue-eos subgroup (Figure 3C). The controlled patients accounted for 27% and 36%, and the uncontrolled patients 46% and 32% of patients in IH-tissue-eos and H-tissue-eos subgroup, respectively (Figure 3A and Table 1). The percentages of patients in the 3 categories of control were not significantly different between IH-tissue-eos and H-tissue-eos subgroups ($p = .251$, Table 1).

We further compared the clinical characteristics between patients with IH-blood-eos and those with H-blood-eos (Figure 1). There were 23 patients with IH-blood-eos and 39 patients with H-blood-eos (Table 2). Compare with the H-blood-eos subgroup, the IH-blood-eos subgroup showed significantly higher percentages of current smoker and asthma, preoperative Lund-Mackay CT score, and tissue eosinophil percentage (Table 2 and Figure 4B,C). There was no significance in gender, age, percentage of allergic rhinitis, and medication length after sinus surgery (Table 2). The controlled patients accounted for 22% and 31%, and the uncontrolled patients 52% and 31% of patients in IH-blood-eos and H-blood-eos subgroup, respectively (Figure 4A and Table 2). The IH-blood-eos subgroup showed a trend toward a higher rate of uncontrolled subjects compared with the H-blood-eos subgroup, although this did not reach statistical significance ($p = .09$, Table 2).

4 | DISCUSSION

Understanding the relationship of eosinophil levels with disease features is important in this field, especially since type 2 inflammation-targeted therapies are now available. Numerous evidences have shown that eosinophil infiltration is an important marker that associated with severe disease and higher recurrence rates after ESS in patients with CRSwNP. However, the range of eosinophilia in polyp tissues and peripheral blood can vary markedly from patient to patient,[23] and patients with intensely high levels of eosinophilia have not previously been studied. To our knowledge, this is the first study that compared the clinical features between patients with intensely high levels of eosinophils and those with levels near the threshold of tissue and blood eosinophilia. In this preliminary study of a prospective cohort of CRSwNP patients, we found that there

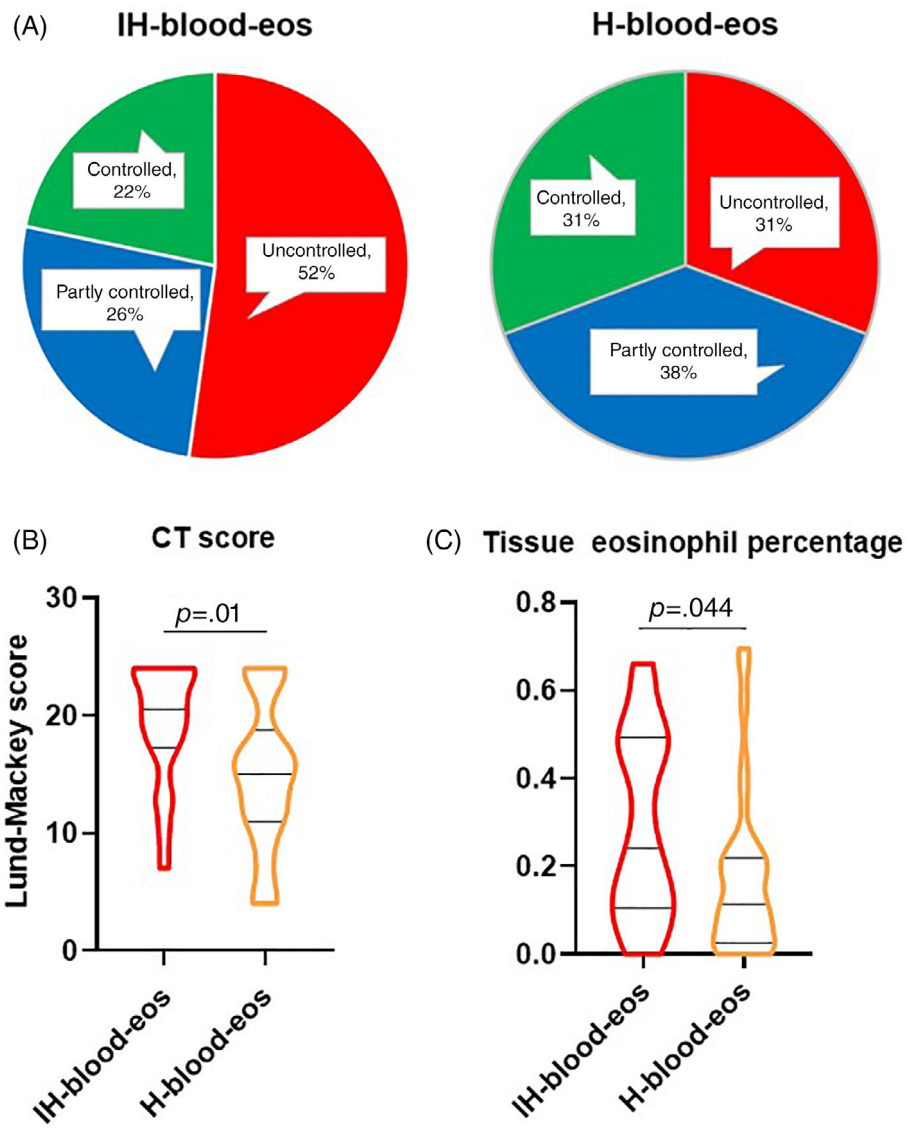

FIGURE 4 Prevalence of uncontrolled CRSwNP (A), CT score (B), and tissue eosinophil percentage (C) in the subgroups with intensely high blood eosinophils (IH-blood-eos) and high blood eosinophils (H-blood-eos)

was a trend of higher rates of uncontrolled disease for patients with higher cut-off values of blood eosinophils, but not tissue eosinophils. We further compared the clinical features between patients with IH-tissue-eos and H-tissue-eos, and between patients with IH-blood-eos and H-blood-eos, and found that the patients with IH-blood-eos had higher percentages of current smoker and asthma, preoperative Lund-Mackay CT score, and tissue eosinophil percentage than those with H-blood-eos. A trend of higher rates of uncontrolled disease was also observed in the IH-blood-eos patients compared to the H-blood-eos patients. Interestingly, a similar trend was not observed between IH-tissue-eos and H-tissue-eos patients. Together, these results suggest that intensely high blood eosinophil count is associated with poorer disease control in patients with CRSwNP after ESS.

Previous studies have evaluated the associations between tissue eosinophilia and surgical treatment response and prognosis in patients with CRSwNP. For example, Tokunaga et al. reported a multicenter retrospective study of 1716 patients showing that individuals with more than 70 eosinophils/HPF in mucosal tissues was characterized with a refractory nature of disease.[24] Lou et al. revealed an eosinophil-dominant CRSwNP, in which tissue eosinophils was more than 54.5% of total inflammatory cells, had a polyp recurrence rate as high as 98.5%.[25] In another report with multivariate analysis, they identified a tissue eosinophil proportion over 27% and a tissue eosinophil count over 55 eosinophils/HPF as the strongest predictors of polyp recurrence after sinus surgery in the Chinese patients with CRSwNP.[26] However, the relationship between the patients with different level of tissue eosinophilia and disease control is still unclear. In the current study, we chose various cut-off values for tissue eosinophilia, ranging from 10% to 50%, to subdivide the retrospective cohort, and found that patients with different tissue eosinophil cut-off values displayed similar rates of uncontrolled disease, suggesting that eosinophils in polyp tissues would not further increase risks for poor disease control when they reach the threshold value of 10%.

Although emerging evidence indicated that blood eosinophil numbers are positively associated with eosinophil levels in nasal

polyps,[12,13,27] there were few studies comparing the difference between blood and tissue eosinophilia in relation to disease control. Recently, our studies revealed that the blood eosinophil count and the tissue eosinophil percentage are independently associated with an increased risk for poor disease control in CRSwNP patients receiving current standard-of-care therapy after adjustments for covariates previously shown to relate to poor treatment outcome. Additionally, prior study showed that the cut-off value of blood eosinophil count (>0.26 $\times$ 10^9/L) might have relatively good, predictive potential in patients with nasal polyps who require surgical treatment.[28] In the present study, we further found that there was no significant difference in the rate of uncontrolled subjects between IH-tissue-eos and H-tissue-eos subgroups, whereas the IH-blood-eos patients had higher rates of uncontrolled subjects and asthma and CT scores than the H-blood-eos patients ($p = .09$, Table 2). These results imply that blood eosinophils might possibly have a larger influence on treatment outcomes and disease severity than tissue eosinophils. Higher blood eosinophils should not only alert the clinician to patients likely to have tissue eosinophilia, but also require the clinician to close follow-up for management to prevent treatment failure.

There are several limitations in this study. First, because of the retrospective nature of the present study, we were unable to assess the subjects' control status with an identical timing after ESS. Since the rate of uncontrolled disease status may increase over time after surgery,[29] significantly different timing of disease control assessment could bias the results. Second, the analyses were based on a single time-point measurement of blood eosinophil count per patient, which ignores the possible fluctuation of inflammatory patterns of patients over time. Third, the sample size of the IH-tissue-eos, H-tissue-eos, IH-blood-eos, and H-blood-eos subgroups is relatively small, since we did not observe significant differences in the percentages of patients in the three categories of control between subgroups. Further studies with large prospective cohorts are warranted to address the above limitations.

5 | CONCLUSION

In summary, by examining subsets of CRSwNP patients with various cut-off values of tissue and blood eosinophilia, our findings suggest that patients with intensely high blood eosinophil count (≥0.6 $\times$ 10^9/L) may be possibly associated with a poorer disease control than those with levels near the threshold of blood eosinophilia (0.2 $\times$ 10^9/L–0.3 $\times$ 10^9/L). Further larger, preferably prospective studies are needed to confirm this relationship.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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