

# Evaluation of nasal symptoms to distinguish eosinophilic from noneosinophilic nasal polyps based on peripheral blood

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## ABSTRACT

**Background:** Patients with eosinophilic chronic rhinosinusitis with nasal polyps (eCRSwNP) have poorer outcomes after endoscopic sinus surgery and a higher recurrence rate.

**Objective:** This study aimed to investigate the profile of clinical symptoms of eCRSwNP and the related risk factors.

**Methods:** We prospectively enrolled 298 inpatients with CRSwNP from February 2019 to December 2019. The patients were divided into eCRSwNP and non-eCRSwNP groups based on the percentage of blood eosinophils; the cutoff value was set at 3.05%. Clinical data on questionnaires, visual analog scale (VAS) scores, and laboratory tests were collected. The differences in clinical symptoms, including nasal congestion, rhinorrhea, olfactory disorders, and head and/or facial pain, between the two groups were analyzed to identify the influential factors. Logistic analysis and receiver operating characteristic curves were used to determine the diagnostic benefit for the specific symptom in the patients in the eCRSwNP group.

**Results:** Nasal congestion and olfactory disorders were significantly different between the eCRSwNP and non-eCRSwNP groups. The patients in the eCRSwNP group more frequently had concerns about olfactory disorders ( $p=0.002$ ), whereas patients in the non-eCRSwNP group mostly had nasal congestion ( $p=0.001$ ). The logistic analysis showed that the primary risk factors for olfactory disorders of eCRSwNP were disease duration ( $p=0.014$ ) and alcohol intake ( $p=0.012$ ). Olfactory disorders were not associated with the disease course of the eCRSwNP group but were correlated with the disease duration of non-eCRSwNP ( $p=0.008$ ). A VAS score for the olfactory disorders of  $>5.75$  could be used to predict the diagnosis of eCRSwNP (area under the curve, 0.674 [95% confidence intervals, 0.559–0.689];  $P<0.001$ ).

**Conclusion:** Olfactory disorder might be the major nasal symptom that could be used to distinguish a peripheral eosinophilia-based definition of eCRSwNP and non-eCRSwNP. The disease duration was a limiting factor for using olfactory to distinguish two subgroups of nasal polyp. The investigation with regard to the accurate time boundary should be further addressed.

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Chronic rhinosinusitis (CRS), which refers to a chronic inflammatory disease of the nasal cavity and sinuses over 3 months, can cause various clinical symptoms, such as nasal congestion and olfactory

disorders.<sup>1</sup> CRS is usually divided into two subtypes: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps. In addition to confirming a diagnosis, endotyping of inflammatory disease is becoming more important because it will guide the integrated therapy. The endotyping approach prompted the idea that disease may share the same mechanism of action, even with a different etiology and final clinical features.<sup>2</sup> Eosinophil, basophil, or neutrophil counts can be subcohorts of CRSwNP, with a similar clinical picture but different biologic and pathogenic mechanisms. The peripheral blood relative proportions of these types of cells would provide prognostic information and rational following-up protocols in the long term.<sup>3</sup>

In general, CRSwNP can be divided into eosinophilic CRSwNP (eCRSwNP) and non-eCRSwNP<sup>4</sup> based on the dominant inflammatory cells, and they have overlapping clinical symptoms, of nasal congestion, olfactory disorders, rhinorrhea, and head or facial pain. Because these two subtypes have different treatment responses and prognoses for drug or surgical

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intervention,<sup>5,6</sup> the first aptitudinal diagnostic impression is valuable for the further guidance for examination and treatment.

To date, studies on the diagnostic identification of eCRSwNP and non-eCRSwNP have been fruitful.<sup>4,7,8,9,10,11</sup> For example, those with peripheral blood eosinophil counts  $\geq 0.215 \times 10^9/\text{L}$  or percentage eosinophils  $\geq 3.05\%$  were classified as eCRSwNP<sup>7</sup>; a differential diagnosis can be made through radiologic features.<sup>8</sup> Moreover, eosinophilic CRS (eCRS) can also be confirmed by tissue eosinophils, *i.e.*,  $\geq 10/\text{hpf}$  (High-power field) ( $\times 400$ ).<sup>9</sup> However, the above predictive diagnoses of eCRSwNP had an economic burden and time lag, and even were invasive. Therefore, this study aimed to identify typical clinical symptoms that were meaningful for the differential diagnoses of eCRSwNP and non-eCRSwNP at the first visit, so that we can confirm the diagnosis and apply the optimal treatment as soon as possible.

## METHODS

### Participants and Study Design

We prospectively analyzed clinical data of adult patients (ages  $\geq 18$  years) who met the diagnosis of CRSwNP. The diagnosis of CRSwNP was based on the standard criteria of the European Position Paper on Rhinosinusitis and Nasal Polyps guidelines.<sup>1</sup> All the enrolled patients had discontinued oral corticosteroids, antihistamines, and leukotriene receptor inhibitors for at least 1 month. The patients were hospitalized and underwent endoscopic sinus surgery at Beijing Tongren Hospital from February 2019 to December 2019. Among 500 invited adult patients with CRSwNP, 144 with the diagnosis of fungal sinusitis or CRS without nasal polyps were excluded; finally, 298 patients were enrolled in this study. Clinical characteristics, chief concerns, laboratory tests, nasal functions, and endoscopic and radiologic scores were collected at the time of admission and were recorded in the patients' medical record system. The visual analog scale (VAS) questionnaire, with an accuracy of 0.1, was completed by the participants, and the items included four clinical symptoms: nasal congestion, rhinorrhea, olfactory disorders, and head and/or facial pain.

Among the 298 patients, 12 did not complete the questionnaires; therefore, 286 questionnaires were obtained and analyzed. We grouped the final 298 patients with CRSwNP into two subgroups, eCRSwNP and non-eCRSwNP. A blood eosinophil percentage  $> 3.05\%$  was set as a cutoff value for distinguishing eCRSwNP and non-eCRSwNP.<sup>7</sup> The clinical characteristics of eCRSwNP and non-eCRSwNP, especially nasal congestion, rhinorrhea, olfactory disorders, and head and/or facial pain, were compared. We also carried out a stratified analysis to further determine the

symptomatic difference based on the clinical duration. This study was approved by the ethics committee of Beijing Tongren Hospital, and written informed consent was obtained from the patients before data collection. X. Pan and Y. Zhang contributed equally to this work.

### Clinical Data Collection

Collected data included basic clinical information, chief concerns, laboratory tests, allergy status, serum total immunoglobulin E (IgE), nasal function, endoscopic examination, and radiologic scores. The basic clinical information included age, gender, disease duration, previous surgery, smoke, alcohol use, and asthma history. The laboratory tests included percentages of blood neutrophils, blood lymphocytes, blood monocytes, and blood eosinophils. The blood samples were taken before surgery and were analyzed by using an automated analyzer. For the patients with CRSwNP, the duration of disease and history of previous nasal surgery or comorbidity with asthma were recorded.

The evidence of nasal polyps was confirmed by using endoscopy in the uni- or bilateral nasal cavity. Nasal resistance was measured by HRR2 four-phase rhinomanometry (RhinoLab GmbH, Rendsburg, Germany) in an examination room at a temperature of  $22^\circ\text{C}$  to  $24^\circ\text{C}$  and 40% to 70% humidity. Nasal resistances were assessed at 75 Pa and 150 Pa, on both sides, and total nasal resistance and unilateral nasal resistance were recorded at each pressure.<sup>9,12</sup> The serum total IgE (KU/L) was evaluated by using ImmunoCap Phadiatop (Pharmacia, Uppsala, Sweden). Before surgery, an endoscopic examination was scored according to the Lund-Kennedy system, and edema, nasal discharge, scarring, and crusting were assessed.<sup>13,14</sup>

Computed tomography (Revolution CT; GE Medical systems, Milwaukee, WI) of paranasal sinuses was performed for all the patients, and scoring was conducted by using the Lund-Mackay system<sup>15</sup>: 0, no soft tissue in the sinus; 1, partial soft tissue; and 2, full of tissue. The ethmoid sinus score (E) divided by mastoid score (M) was determined: E stands for the sum of the anterior and posterior ethmoid sinus scores on both sides and M stands for the sum of bilateral maxillary sinus scores. The sensitization status was confirmed based on ImmunoCap Phadiatop, and the aeroallergens used for tests included house-dust mite (Der f and Der p), seasonal grass pollens (*e.g.*, giant ragweed, mugwort, Lamb's quarters, humulus, *Chenopodium album*), animal hair (especially dog and cat), molds (indoor and outdoor mustiness or floricultural environment), and cockroach. The participants were considered to be sensitized to allergens when the serum IgE level was  $\geq 0.35$  kU/L.

Table 1 Clinical characteristics of the participants

| Variable                                     | eCRSwNP (n = 152)   | Non-eCRSwNP (n = 146) | p                |
|----------------------------------------------|---------------------|-----------------------|------------------|
| Age, mean $\pm$ SD, y                        | 43.16 $\pm$ 11.58   | 44.88 $\pm$ 14.71     | 0.192            |
| No. men/women                                | 94/58               | 48/25                 | 0.483            |
| Disease duration, mean $\pm$ SD, y           | 5.67 $\pm$ 6.06     | 6.62 $\pm$ 6.84       | 0.469            |
| Previous FESS surgery, n (%)                 | 20 (13.2)           | 9 (12.3)              | 0.830            |
| Smoker, n (%)                                | 28 (18.4)           | 15 (20.5)             | 0.644            |
| Alcoholics, n (%)                            | 13 (8.55)           | 10 (13.7)             | 0.158            |
| History of asthma, n (%)                     | 21 (13.8)           | 3 (4.28)              | <b>0.004</b>     |
| Allergy status                               | 32 (28.83)          | 19 (31.67)            | 0.700            |
| Blood eosinophils, mean $\pm$ SD             | 7.73 $\pm$ 9.12     | 1.73 $\pm$ 0.80       | <b>&lt;0.001</b> |
| Blood neutrophils, mean $\pm$ SD             | 54.80 $\pm$ 31.34   | 59.83 $\pm$ 9.22      | <b>&lt;0.001</b> |
| Blood monocytes, mean $\pm$ SD               | 6.99 $\pm$ 4.27     | 6.21 $\pm$ 1.45       | <b>0.007</b>     |
| Serum total IgE level, mean $\pm$ SD, KU/L   | 209.82 $\pm$ 287.30 | 199.04 $\pm$ 499.99   | <b>0.002</b>     |
| Blood lymphocyte, mean $\pm$ SD              | 32.93 $\pm$ 7.34    | 31.44 $\pm$ 8.64      | 0.070            |
| Eosinophil exfoliated cells, mean $\pm$ SD   | 1.56 $\pm$ 0.50     | 1.81 $\pm$ 0.40       | <b>&lt;0.001</b> |
| Lund-Kennedy endoscopic score, mean $\pm$ SD | 6.82 $\pm$ 2.46     | 7.10 $\pm$ 2.85       | 0.487            |
| E/M ratio*, mean $\pm$ SD                    | 2.26 $\pm$ 0.74     | 1.87 $\pm$ 0.96       | <b>&lt;0.001</b> |
| Lund-Mackay CT score (total), mean $\pm$ SD  | 15.51 $\pm$ 6.33    | 14.31 $\pm$ 6.56      | 0.219            |

eCRSwNP = Eosinophilic chronic rhinosinusitis with nasal polyps; SD: standard deviation; FESS = Functional endoscopic sinus surgery; IgE = immunoglobulin E; E/M; ethmoid sinus score (E) divided by mastoid score (M).

Analysis method: Mann-Whitney U test.

p values in bold showed the significant difference between eCRSwNP and non-eCRSwNP.

## Statistical Analysis

Data were analyzed by using SPSS version 23.0 software (IBM Corp, Armonk, NY). All data are expressed as median and interquartile range or number and percentage. The Mann-Whitney U test for unpaired comparisons was used for the comparison between the groups. The relationship between the chief concerns and the clinical information was evaluated by using relevance analysis and logistic regression analysis. Odds ratios (OR) and 95% confidence intervals were calculated by using the logistic regression model. The receiver operating characteristic (ROC) curve was used to distinguish eCRSwNP and non-eCRSwNP. An area under the curve (AUC) of  $>0.9$  was defined as the higher predictive value, an AUC of 0.7–0.9 as the moderate value, and an AUC of 0.5–0.6 as the lower value. The optimal cutoff point was the one that corresponded to the data with the highest sensitivity and specificity;  $p < 0.05$  was considered significant.

## RESULTS

### Demographics of the Participants

This study observed a total of 298 patients with CRSwNP, including 152 in the eCRSwNP group (51%) and 146 in the non-eCRSwNP group (49%). The age was similarly distributed (40 to 50 years) in both groups ( $p = 0.192$ ), and the male-female ratios in both

groups were nearly 2:1. The patients of the two groups of CRSwNP had different durations (from at least 3 months to at most 40 years) but not significant ( $p = 0.496$ ) as well as tobacco use (18.4% versus 20.5%;  $p = 0.664$ ) or alcohol use (8.55% versus 13.7%;  $p = 0.158$ ). Notably, the patients in the eCRSwNP group were more likely to have a history of asthma versus the patients in the non-eCRSwNP group (13.8 versus 4.28%;  $p = 0.004$ ). The patients in both groups were in the high sensitive state (28.83% versus 31.67%;  $p = 0.700$ ), with no significant difference.

Moreover, some laboratory test results revealed distinct differences between the eCRSwNP and non-eCRSwNP groups. The  $p$  value between the two groups for the percentages of blood eosinophils, blood neutrophils, and blood monocytes, and the serum total IgE level were 0.000, 0.000, 0.007, and 0.002, respectively. The difference in the ethmoid sinus score (E) divided by mastoid score (M) ratio between the two groups was significant ( $p = 0.000$ ) but not the total Lund-Kennedy endoscope scores ( $p = 0.487$ ) and the Lund-Mackay CT scores ( $p = 0.219$ ). The details of the demographic and clinical characteristics are shown in Table 1.

### Comparison of Profiles of Nasal Symptoms between eCRSwNP and Non-eCRSwNP Groups

A total of 286 patients completed the questionnaires, including 148 patients in the eCRSwNP group and

**Table 2 Comparison of profiles of nasal symptoms between patients in the eCRSwNP group and patients in the non-eCRSwNP group**

| Variables                                | ECRSwNP (n = 148) | Non-eCRSwNP (n = 138) | p                |
|------------------------------------------|-------------------|-----------------------|------------------|
| VAS scores, mean $\pm$ SD                |                   |                       |                  |
| Nasal congestion                         | 5.70 $\pm$ 3.14   | 6.31 $\pm$ 2.93       | 0.113            |
| Rhinorrhea                               | 3.82 $\pm$ 3.11   | 3.27 $\pm$ 3.33       | 0.066            |
| Olfactory disorders                      | 6.50 $\pm$ 3.61   | 4.87 $\pm$ 3.65       | <b>&lt;0.001</b> |
| Head and/or facial pain                  | 2.34 $\pm$ 2.68   | 2.25 $\pm$ 2.71       | 0.323            |
| Symptom with the highest severity, n (%) |                   |                       |                  |
| Nasal congestion                         | 57 (38.5)         | 80 (58.0)             | <b>0.001</b>     |
| Rhinorrhea                               | 22 (14.9)         | 22 (15.9)             | 0.801            |
| Olfactory disorders                      | 85 (57.4)         | 54 (39.1)             | <b>0.002</b>     |
| Head and/or facial pain                  | 13 (8.78)         | 14 (10.1)             | 0.695            |

eCRSwNP = Eosinophilic chronic rhinosinusitis with nasal polyps; VAS = visual analog scale; IQR = interquartile range.

Analysis method: Mann-Whitney U test.

p values in bold showed the significant difference between eCRSwNP and non-eCRSwNP.  $P < 0.05$  was statistically significant.

**Table 3 Diagnostic predictive values of parameters**

| Parameter               | AUC   | 95% CI      | Cutoff Value | Sensitivity | Specificity | p                |
|-------------------------|-------|-------------|--------------|-------------|-------------|------------------|
| Olfactory disorders     | 0.624 | 0.559–0.689 | 5.75         | 0.662       | 0.594       | <b>&lt;0.001</b> |
| Head and/or facial pain | 0.563 | 0.496–0.630 | 0.85         | 0.743       | 0.406       | 0.067            |
| Rhinorrhea              | 0.534 | 0.466–0.601 | 0.15         | 0.797       | 0.319       | 0.327            |
| Nasal congestion        | 0.446 | 0.379–0.512 | 0.3          | 0.939       | 0.072       | 0.113            |

AUC = Area under the curve; CI = confidence interval.

138 patients in the non-eCRSwNP group. Olfactory disorder was the symptom with the most distinct difference between the two groups and was the unique symptomatic concern that was significantly different between the two groups ( $p = 0.000$ ). The VAS scores of nasal congestion, rhinorrhea, olfactory disorder, and head and/or facial pain did not significantly differ between these two groups. Further evaluation of nasal congestion by using rhinomanometry of uni- or bilateral nasal resistance at either 75 pa or 150 pa was not significantly different between the two groups (see Supplemental Table 1).

Moreover, patients in the two groups had different primary symptoms. The patients in the eCRSwNP group were more likely concerned by olfactory disorders ( $p = 0.002$ ), and the patients in the non-eCRSwNP group were more likely to be concerned by nasal congestion ( $p = 0.001$ ). Details of the comparison of nasal symptoms are shown in Table 2. By using the ROC curves, we further explored that, among the four symptoms, olfactory disorder was the only valuable clinical marker for the predictive diagnosis of eCRSwNP. The details are shown in Table 3, and the ROC curves are shown in Fig. 1. The

AUC of olfactory disorder (AUC, 0.642) was higher than those of other symptoms, with a sensitivity of 0.662 and specificity of 0.594 (95% confidence interval, 0.559–0.689;  $p = 0.000$ ).

#### Factors Associated with Olfactory Function in the Patients in the eCRSwNP and Non-eCRSwNP Groups

To further determine the factors associated with olfactory function in CRSwNP, a relevance analysis and logistic regression analysis were conducted based on between-group comparison analysis. Relevance analysis revealed that smell loss was related to blood neutrophilic percentage ( $p = 0.031$ ), blood lymphocyte percentage ( $p = 0.014$ ), blood neutrophilic absolute counts ( $p = 0.013$ ) in the patients in the eCRSwNP group. In the non-eCRSwNP group, olfactory disorders were related to disease duration ( $p = 0.020$ ) and alcohol intake ( $p = 0.018$ ). Further, the multiple logistic regression found that both CRSwNP group and non-eCRSwNP group were significantly correlated with disease duration (OR 11.23 [ $p = 0.014$ ]; OR 1.21 [ $p = 0.008$ ]). These details are shown in Table 4.

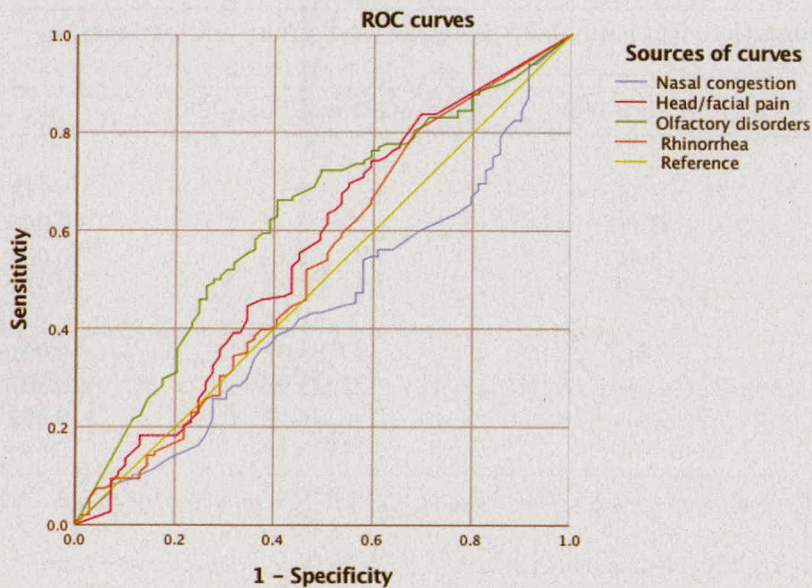


**Figure 1.** The area under the characteristic (AUC) curves of the four symptoms. The AUC of olfactory disorder (AUC, 0.642) was higher than those of other symptoms.

**Table 4** Factors associated with olfactory function in the patients with CRSwNP

| Variables                                              | Relevant Analysis |          | Logistic Analysis |            |              |
|--------------------------------------------------------|-------------------|----------|-------------------|------------|--------------|
|                                                        | Coefficient       | <i>p</i> | OR                | 95% CI     | <i>p</i>     |
| Total CRSwNP                                           |                   |          |                   |            |              |
| Disease duration                                       | 0.132             | 0.026    | 1.23              | 0.69–2.20  | <b>0.014</b> |
| Blood eosinophilic percentage (%)                      | 0.152             | 0.01     | 2.09              | 0.94–4.67  | <b>0.001</b> |
| Alcoholics                                             | –0.197            | 0.011    | 6.63              | 1.49–29.66 | <b>0.012</b> |
| eCRSwNP                                                |                   |          |                   |            |              |
| Blood neutrophilic percentage (%)                      | 0.177             | 0.031    | 0.754             | 0.179–3.18 | 0.807        |
| Blood lymphocyte percentage (%)                        | –0.201            | 0.014    | 2.20              | 0.72–6.70  | 0.228        |
| Blood neutrophil absolute counts (10 <sup>9</sup> g/L) | 0.205             | 0.013    | 1.48              | 0.35–6.37  | 0.472        |
| Non-eCRSwNP                                            |                   |          |                   |            |              |
| Disease duration                                       | 0.266             | 0.020    | 1.21              | 0.53–2.77  | <b>0.008</b> |
| Alcoholics                                             | –0.201            | 0.018    | 7.34              | 1.63–33.06 | <b>0.009</b> |

CRSwNP = Chronic rhinosinusitis with nasal polyps; OR = odds ratio; CI = confidence interval; eCRSwNP = Eosinophilic chronic rhinosinusitis with nasal polyps.

Analysis method: Relevant analysis and logistic analysis.

*p* values in bold showed that Disease duration, blood eosinophilic percentage, and alcoholics were factors with significant difference for the CRSwNPs. Disease duration, alcoholics were the significant difference for the non-eCRSwNPs. *P* < 0.05 was statistically significant.

#### Effects of Disease Duration on Olfactory Dysfunction in the Patients in the eCRSwNP Group and Patients in the Non-eCRSwNP Group

To further examine the association of olfactory dysfunction with disease duration in eCRSwNP and non-eCRSwNP, we classified the patients into four subgroups: disease duration of <1 year, 1–5 years, 6–10 years, and >10 years. The results revealed significant differences between the patients in the eCRSwNP group and patients in the non-eCRSwNP group in three of the

subgroups < 10 years (*p* = 0.013, *p* = 0.001, *p* = 0.011). However, the difference between the two groups with the > 10-year duration was not significant (*p* = 0.264). Moreover, blood eosinophilic percentage (OR, 2.09; *p* = 0.001) and eosinophilic absolute counts (OR, 2.63; *p* = 0.001) were correlated with a loss of smell in the overall CRSwNP group. In addition, alcohol intake (OR, 7.34; *p* = 0.009) was another apparent influential factor for olfactory disorder in patients in the non-eCRSwNP group. The details are presented in Table 5.

Table 5 Comparison of nasal symptoms between patients in the eCRSwNP group ( $n = 148$ ) and patients in the non-eCRSwNP group ( $n = 138$ ) based on disease duration

| Variable                | VAS Score, median (Mean $\pm$ SD) |                 | <i>p</i>     |
|-------------------------|-----------------------------------|-----------------|--------------|
|                         | eCRSwNP Group                     | Non-eCRSwNP     |              |
| Duration: < 1 y         |                                   |                 |              |
| Total no. patients      | 26                                | 30              |              |
| Nasal congestion        | 4.50 $\pm$ 2.97                   | 4.93 $\pm$ 3.42 | 0.633        |
| Rhinorrhea              | 3.11 $\pm$ 2.83                   | 2.49 $\pm$ 3.05 | 0.268        |
| Olfactory disorders     | 6.07 $\pm$ 3.67                   | 3.35 $\pm$ 3.44 | <b>0.013</b> |
| Head and/or facial pain | 2.75 $\pm$ 3.70                   | 1.47 $\pm$ 1.96 | 0.071        |
| Duration: 1–5 y         |                                   |                 |              |
| Total no. patients      | 66                                | 44              |              |
| Nasal congestion        | 5.48 $\pm$ 3.42                   | 6.24 $\pm$ 2.98 | 0.386        |
| Rhinorrhea              | 4.24 $\pm$ 3.24                   | 3.17 $\pm$ 2.80 | 0.068        |
| Olfactory disorders     | 6.76 $\pm$ 3.49                   | 5.18 $\pm$ 3.35 | <b>0.010</b> |
| Head and/or facial pain | 2.40 $\pm$ 2.63                   | 2.45 $\pm$ 2.72 | 0.864        |
| Duration: 6–10 y        |                                   |                 |              |
| Total no. patients      | 42                                | 44              |              |
| Nasal congestion        | 6.54 $\pm$ 2.85                   | 6.91 $\pm$ 2.35 | 0.782        |
| Rhinorrhea              | 3.62 $\pm$ 3.18                   | 3.79 $\pm$ 3.81 | 0.696        |
| Olfactory disorders     | 6.52 $\pm$ 3.78                   | 4.46 $\pm$ 3.57 | <b>0.011</b> |
| Head and/or facial pain | 2.47 $\pm$ 2.87                   | 2.30 $\pm$ 3.07 | 0.266        |
| Duration: > 10 y        |                                   |                 |              |
| Total no. patients      | 14                                | 20              |              |
| Nasal congestion        | 11.06 $\pm$ 17.37                 | 7.19 $\pm$ 2.54 | 0.368        |
| Rhinorrhea              | 3.76 $\pm$ 2.68                   | 3.54 $\pm$ 3.61 | 0.546        |
| Olfactory disorders     | 12.40 $\pm$ 25.47                 | 7.34 $\pm$ 3.51 | 0.264        |
| Head and/or facial pain | 2.22 $\pm$ 3.15                   | 2.89 $\pm$ 2.64 | 0.158        |

eCRSwNP = Eosinophilic chronic rhinosinusitis with nasal polyps; VAS = visual analog scale; IQR = Inter quartile range. *p* values in bold showed that olfactory disorders were significantly different between the eCRSwNP and non-eCRSwNP in duration <1y, 1–5, and 6–10 y.  $P < 0.05$  was statistically significant.

## DISCUSSION

Olfactory disorder is an important clinical manifestation of CRSwNP. European and American investigators have statistically shown that ~14% and 10% of patients with CRS, in the Europe and in America, respectively, had progressive olfactory dysfunction.<sup>1,15,16</sup> Although an olfactory disorder is not fatal, it could seriously lower the quality of life and result in loss of appetite, malnutrition, immunity dysfunction, and even food poisoning due to accidental consumption of spoiled food.<sup>17,18</sup> Multiple cytokines play roles in the pathogenesis of eCRS, by keeping the high levels of circulatory eosinophils and tissue eosinophils as classic features. Cytokines are essential for hematopoietic cell development, differentiation, and maturation. Interleukin (IL) 3, IL-5, and granulocyte-macrophage-colony stimulating factor played a role in the regulation of eosinophil development.

IL-5 made the eosinophils mature and drove them into the bone marrow towards the circulation. Then eosinophils accumulated rapidly in tissues, producing edema, bronchoconstriction, and chemotaxis. IL-9 regulates

granulocytopoiesis in allergic inflammation. IL-13 upregulates the levels of  $\beta$ -catenin, which enhanced the cell-cell adhesion. IL-16 provoked the migration of persistently activated eosinophils. IL-25, IL-33 initiated Th2 inflammation and eosinophilia. IFN  $\gamma$  and TGF  $\beta$  played a downregulating role in eCRSwNP. Therefore, cytokines formed a far more complex biochemical network in the production, activation, and regulation of eosinophils.<sup>19</sup>

Results of studies showed that the most common clinical symptom of eCRSwNP are olfactory disorders,<sup>20,10</sup> and eCRSwNP was usually resistant to drug therapy and surgical treatment, and was prone to relapse after treatment. Therefore, eCRSwNP, an important category of refractory rhinosinusitis, had become the “bottleneck” in the treatment of eosinophilic nasal polyps with functional endoscopic sinus surgery.<sup>10</sup> To date, researchers have developed a variety of diagnostic approaches for eCRSwNP, such as blood routine tests, radiologic examinations, and tissue histopathology. The reason for the selection of peripheral blood eosinophilia as the criterion was that, such a simple classification method was more

applicable in the outpatient clinic and thus we would easily find the patients who are susceptible and who would not undergo surgery for biopsy and gave them advice concerning further precise treatment and possible outcomes. Based on such a criterion, we planned to diagnose eCRSwNP by recognizing the primary chief complaint.

A total of 298 patients with CRSwNP were prospectively analyzed in our study, and the clinical characteristics of eCRSwNP and non-eCRSwNP were collected, described, and analyzed to explore the initial diagnostic tendency. In our study, most patients with CRSwNP were ages between 40 and 50 years, with a male dominance. Patients with eCRSwNP had a familiar history of asthma, which was consistent with those in many previous studies.<sup>11,22</sup> In addition, on computed tomography, were manifestation of eCRSwNP with features of the centralization of polyps and edema mucosa in the ethmoid sinus and the olfactory cleft (OC) region, whereas in the non-eCRSwNP group, it was predominantly observed in the maxillary sinus, which was similar to that in previous studies.<sup>8,23</sup> Notably, patients in the eCRSwNP group were mostly concerned, in the early days, about an olfactory disorder; patients in the non-eCRSwNP group commonly presented, with nasal congestion with olfactory sensation worsening over time. Therefore, olfactory dysfunction might be the most important clinical symptom in patients with eCRSwNP and in those in the non-eCRSwNP group.

In our study, the patients in the eCRSwNP group had more severe olfactory disorders than did those in the non-eCRSwNP group. The number and severity of the symptoms were significantly higher in the patients in the eCRSwNP group than in the patients in the non-eCRSwNP group. By multiple regression analysis, we found that the high eosinophilic level in the peripheral blood was an independent risk factor for olfactory dysfunction in the patients with CRSwNP. The higher the eosinophil level, the more severe the olfactory dysfunction would be.

Haruna et al<sup>18</sup> reported that olfactory dysfunction was more significant when there was a large number of eosinophils in the ethmoid sinus mucosa than when there was a small number of eosinophils in the tissue. Mori et al<sup>24</sup> observed that patients with eCRS had more severe olfactory dysfunction than did the patients with non-eCRS, and smoking was a risk factor for olfactory dysfunction. Therefore, it was believed that patients with eCRSwNP were more likely to experience a loss of smell, probably due to the high eosinophilic level. Furthermore, the ROC curves, with 5.75 as the cutoff value, revealed the significance of olfactory dysfunction in clinical symptoms. In a word if the VAS score of olfactory disorders was > 5.75, the patient probably had eCRSwNP, and the symptomatic marker for olfactory dysfunction would be practical and instructive.

The analysis of the risk factors found that olfactory disorders were correlated with the eosinophilic levels and

alcohol intake but not with the disease duration in the patients in the eCRSwNP group. Traditionally, the olfactory disorder of eCRSwNP is caused by complicated mechanisms, and nasal obstruction and inflammation were the two major causes. The obstructive effect of edema of the sinonasal mucosa or nasal polyposis blocked odorants to the OC, which leads to olfactory mechanical conductive dysfunction.<sup>11</sup> Furthermore, the inflammation of the olfactory neuroepithelium in the sinonasal cavity was another keystone of olfactory disorder which was worthy of attention..

Olfactory neurons and the supporting cells within the epithelium of the nasal vault extend along the OC, which include the superior aspect of the nasal septum, middle turbinate, superior turbinate, and cribriform plate. The poorer transport of odorant caused by inflammation of the OC neuroepithelium results in chemical reactive disorders. Moreover, eosinophils release neurotoxic mediators, *e.g.*, eosinophilic-derived neurotoxin and may directly destroy the olfactory neurons.<sup>5,11</sup> Results of studies proved that, in eCRSwNP, polyps and edema usually located around the ethmoid sinus and the OC, which featured with high density in such portions, instead of maxillary sinus.<sup>8,25</sup>

However, such a radiologic feature was not typical in our study, and we supposed that the inflammation mechanism played a critical role in olfactory disorders. In recent years, more studies have focused on alcohol-related olfactory deficits, which may be due to the impaired olfactory sensitivity, functional determination, and cognitive process.<sup>24</sup> Alcohol hyperresponsiveness was considered significantly more prevalent in patients with CRSwNP who experience a recurrence and in those with severe symptoms, *e.g.*, loss of smell.

Therefore, the alcohol usage to lower the responsiveness may be a span-new way to improve the symptom of olfactory disorder in CRSwNP.<sup>26</sup> In contrast, olfactory disorders were related to the disease duration in patients in the non-eCRSwNP group. The longer the duration, the more severe the hyposmia would be. Further, stratified analysis of the disease duration showed that, when the disease duration was < 10 years, the patients in the eCRSwNP group had more apparent olfactory disorders, whereas patients in the non-eCRSwNP group mainly had nasal congestion. However, when the disease duration was > 10 years, the symptoms of olfactory disorders became confusing in both groups. These findings indicated that, with the progression of the disease, olfactory dysfunction became more significant in the patients in the non-eCRSwNP group, probably because the reduplicate stimulation destroyed the epithelium in the context of chronic inflammation.<sup>25,27</sup>

To sum, if a patient with CRSwNP and with the first or major concern about the olfactory disorder, it would be necessary to test his peripheral blood to certify the status of peripheral eosinophilia. If so, the immediate management of

nasal spray of steroid or even oral glucocorticosteroids can be the first and effective line of medical therapy to control sinonasal inflammation.<sup>25</sup> The possible complication of asthma or upper airway hypersensitivity should be considered and paid attention to at the meanwhile. Endoscopic sinus surgery, together with topical glucocorticosteroid treatments after endoscopic sinus surgery should be the routine therapies for such eCRSwNP.

There were some limitations in the present study. First, the sample size was limited, so that the disease duration could not be further subdivided, which probably decreased the accuracy of the predictive analysis. Further studies with a large sample size are needed to identify an accurate time boundary for better distinguishing between eCRSwNP and non-eCRSwNP. Second, only subjective judgments of VAS scores were used for the diagnosis of olfactory disorder, and we would like to combine qualitative olfactory tests to improve the diagnostic value once the tests are available in China or we will try to collaborate with international partners in the future.

Third, the diagnostic criteria used in this study were based only on blood eosinophilia because the correlations between blood eosinophilia and tissue eosinophilia in patients with eCRSwNP had previously been elaborated by Hu et al.,<sup>7</sup> and they had concluded that the criterion of a blood eosinophil percentage  $\geq 3.05\%$  satisfied sensitivity and specificity for the diagnosis of tissue-based eCRSwNP. Recently European Position Paper on Rhinosinusitis and Nasal Polyps 2020<sup>9</sup> supported local tissue eosinophilia as the criterion for eCRS, with the cut-off value of  $< 10$  eosinophils/hpf. Nevertheless, the cut-off was less clearly defined in Asians, and can vary from 5 to  $>100$  eosinophils/hpf. Further study on the Chinese-specific tissue eosinophilia criterion based eCRS and the profiles of olfactory disorder should be addressed.

## CONCLUSION

Olfactory disorder might be the major nasal symptom that could be used to distinguish eCRSwNP and non-eCRSwNP in terms of peripheral eosinophilia. However, the duration of disease was a limiting factor for using olfactory to help distinguish the two subgroups of nasal polyps, and the investigation with regard to the accurate time boundary should be further addressed.

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