Olfactory Disorder is The Specific Symptom to Distinguish Eosinophilic From Non-Eosinophilic Nasal Polyps

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Research

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

Methods: We prospectively enrolled 298 CRSwNP inpatients from February 2019 to December 2019. Patients were divided into eCRSwNP and non-eCRSwNP groups based on the percentage of blood eosinophils. Clinical data on questionnaires, visual analogue scale (VAS) scores, and laboratory tests were collected. The differences in clinical symptoms, including nasal congestion, rhinorrhea, olfactory disorders, and head/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 eCRSwNP patients.

Results: Of the four major clinical symptoms, nasal congestion and olfactory disorders were significantly different between eCRSwNP and non-eCRSwNP groups. Patients with eCRSwNP more frequently complained about olfactory disorders ($P = 0.002$), while patients with non-eCRSwNP 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 eCRSwNP but were correlated with the disease duration of non-eCRSwNP ($P = 0.008$). When the clinical duration was less than 10 years, there was a significant difference in olfactory disorders between eCRSwNP and non-eCRSwNP groups ($P < 0.01$). However, when the clinical duration was over 10 years, the difference was not statistically significant ($P = 0.264$). The VAS score of olfactory disorders of over 5.75 could be used to predict the diagnosis of eCRSwNP (area under the curve 0.674, 95% confidence intervals: 0.559–0.689, $P = 0.000$).

Conclusions: Olfactory disorder was the major nasal symptom that could be used to distinguish eCRSwNP and non-eCRSwNP. ECRSwNP patients were more prone to have olfactory dysfunction. Our findings suggest that evaluation of nasal symptoms will help diagnose eCRSwNP and determine subsequent clinical treatment strategies.

Background

Chronic rhinosinusitis (CRS), which refers to a chronic inflammatory disease of the nasal cavity and sinuses over 12 months, can cause various clinical symptoms such as nasal congestion and olfactory disorders (1). It is usually divided into two subtypes: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps. Generally, CRSwNP requires surgical intervention and is known to have two subtypes, eosinophilic CRSwNP (eCRSwNP) and non-eosinophilic CRSwNP (non-eCRSwNP) (2); eCRSwNP is characterized by polarization of T helper 2 and expression of interleukin (IL)-4, IL-5, and IL-13 (3, 4), and non-eCRSwNP is characterized by IL-1, Interferon-gamma, insulin-like growth factor (IGF)-1, IGF-10, and IL-17-mediated cluster of differentiation 8 inflammation. They have overlapped clinical symptoms; for

example, they both present with nasal congestion, olfactory disorders, rhinorrhea, and head or facial pain. In addition, they have different treatment responses and prognosis for drug or surgical intervention (5, 6). Therefore, the first aptitudinal diagnostic impression for these two subtypes is valuable for the further guidance of examination and treatment. To date, studies on diagnostic identification of eCRSwNP and non-eCRSwNP have been very fruitful. For example, those with peripheral blood eosinophil counts ≥ 0.215 × 109/L or eosinophil percent ≥ 3.05% are classified as having eCRSwNP (7); differential diagnosis can be made through radiologic features: when the cutoff ratio of the ethmoid sinus score to the maxillary sinus score is over 2.59, the diagnosis of eCRSwNP is highly expected (8). However, the above predictive diagnoses of eosinophilic CRSwNP are associated with economic burden and time lag. Therefore, this study aimed to identify typical clinical symptoms that are meaningful for the differential diagnosis of eCRSwNP and non-eCRSwNP. The present findings could be used to guide the effective personalized treatment, thereby shortening the treatment time and improving the prognosis.

Methods

Participants and study design

We retrospectively analyzed clinical data of adult patients (age ≥ 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 (1). All the enrolled patients were hospitalized and underwent endoscopic sinus surgery at Beijing Tongren hospital from February 2019 to December 2019. Among 500 invited adult CRSwNP patients, 144 patients with the diagnosis of fungal sinusitis or CRS without nasal polyps were excluded, and 298 were enrolled in this study. The data of clinical characteristics, chief complaints, laboratory tests, nasal functions, and endoscopic and radiologic scores were collected. The visual analogue scale (VAS) questionnaire with the accuracy of 0.1 was completed by participants, and the items included various clinical symptoms, such as nasal congestion, rhinorrhea, olfactory disorders, and head/facial pain. Among the 298 patients, 12 did not complete the questionnaires; therefore, 286 questionnaires were obtained and analyzed. We grouped the final 298 CRSwNP patients into two subgroups, eosinophilic and non-eosinophilic CRSwNP groups. The blood eosinophil percentage higher than 3.05% was set as a cutoff value for distinguishing eosinophilic and non-eosinophilic NP (7). Clinical characteristics of eosinophilic and non-eosinophilic NP, especially nasal congestion, rhinorrhea, olfactory disorders, and head/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 patients before data collection.

Clinical data collection

Collected data included basic clinical information, chief complaints, laboratory tests, allergy status, serum total IgE, nasal functions, and endoscopic and radiologic scores. The basic clinical information included age, sex, disease duration, previous surgery, smoke, alcohol, and asthma history. The laboratory

tests included blood neutrophil percent, blood lymphocyte percent, blood monocyte percent, and blood eosinophil percent. The blood samples were taken during the physical examination and before surgery and were analyzed by an automated analyzer. For NP patients, the duration of disease and history of prior nasal surgery or comorbidity with asthma were recorded. The evidence of nasal polyps was confirmed under endoscopy in the unilateral 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 °C to 24 °C and 40% to 70% humidity. Nasal resistances were assessed at 75 Pa and 150 Pa, respectively, and total nasal resistance and unilateral nasal resistance were recorded at each pressure (9). The serum total IgE (kU/l) was evaluated by Immuno-Cap Phadiatop (Pharmacia, Uppsala, Sweden). Pre-operatively, an endoscopic examination was scored according to the Lund–Kennedy system, and edema, nasal discharge, scarring, and crusting were assessed (10). Computed tomography (Philips Health Care, Best, The Netherlands) of paranasal sinuses was performed for all patients, and scoring was conducted using the Lund–Mackay system (11): no soft tissue in the sinus, scores 0; partial soft tissue, score 1; and full of tissue, score 2. Ethmoid sinus scores (E) were divided by mastoid scores (M) to calculate E/M, in which E stands for the sum of anterior and posterior ethmoid sinus scores on both sides and M stands for the sum of bilateral maxillary sinus scores. Allergy status was confirmed based on Immuno-Cap Phadiatop (Pharmacia, Uppsala, Sweden) (cutoff ≥ 0.35 kU/mL). Nasal cells were collected from both middle turbinates with scrubs (Heinz Herenz, Hamburg, Germany) and smeared on 2 slides with some drops of distilled water. The samples of each group were collected on the same day. The slides were fixed with 80% cold methanol for 24 h; 10 min later, the slides were placed in 80 ml glass beakers with 5.0 M HCl at room temperature for 30 min, rinsed with distilled water for 3 min, stained with Schiff's reagent (Sigma–Aldrich, Steinheim, Germany) for 90 min, washed for 5 min with running water, and then counterstained with 0.2% (wt/vol) Light Green (Sigma–Aldrich, Steinheim, Germany) for 20 s. For each participant, ≥ 2000 nasal cells were evaluated. Both scorers participated in the preliminary stage of the international buccal MN cellular assay scoring exercise.

Statistical analysis

Data were analyzed 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 groups. The relationship between chief complaints and clinical information was evaluated by relevance analysis and logistic regression analysis. Odds ratios (OR) and 95% confidence intervals (CI) were calculated with 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 the moderate value, and an AUC of 0.5-0.6 the lower value. The optimal cutoff point was the one corresponding to the data with the highest sensitivity/specificity. *P values* < 0.05 were considered significant.

Results

Demographics of participants

This study observed a total of 298 CRSwNP patients, including 152 eosinophilic NP patients (51%) and 146 non-eosinophilic patients (49%). The age was similar distributed (forty to fifty years) in both groups ($P = 0.192$), and the male/female ratio was nearly 2:1 in both groups. Patients had CRSwNP for quite different durations (from at least 3 months to at most 40 years). However, there were no significant differences in disease duration ($P = 0.496$), as well as tobacco (18.4% vs 20.5%, $P = 0.664$) or alcohol (8.55% vs 13.7%, $P = 0.158$) intake, between the two groups. The eCRSwNP patients tended to undergo more endoscopic surgery in the past years, but the difference was not significant ($P = 0.83$). Notably, eCRSwNP patients were more likely to have history of asthma than non-eCRSwNP patients (13.8% vs 4.28%, $P = 0.004$). In addition, non-eCRSwNP patients seemed to be weighed more than did eCRSwNP patients ($P = 0.048$). Patients in both groups were in the allergy status (28.83% vs 31.67%, $P = 0.700$), and the difference was not significant between the two groups. Moreover, some laboratory tests revealed distinct differences between eCRSwNP and non-eCRSwNP groups. The P-value between the two groups for blood eosinophil percent, blood neutrophil percent, blood monocyte percent, and serum total IgE were 0.000, 0.000, 0.007, and 0.002, respectively. Furthermore, eCRSwNP patients had more eosinophils and exfoliated cells ($P = 0.000$). The difference in the E/M ratio between the two groups was significant ($P = 0.000$), while differences in total Lund–Kennedy endoscopes score ($P = 0.487$) and Lund–Mackay CT scores were not ($P = 0.219$). The details of demographic and clinical characteristics are displayed in Table 1.

Table 1
Clinical characteristics of participants.

Variables	ECRSwNP (N = 152)	Non-eCRSwNP (N = 146)	*P values*
Age (years), mean (SD)	43.16 ± 11.58	44.88 ± 14.71	0.192
Sex (male/female), n	94/58	48/25	0.483
Disease duration (years)	5.67 ± 6.06	6.62 ± 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
Drinker, n (%)	13 (8.55%)	10 (13.7%)	0.158
Asthma history (%)	21 (13.8%)	3 (4.28%)	**0.004**
Allergy status, +/-(%)	32 (28.83%)	19 (31.67%)	0.700
Blood eosinophil percent (%)	7.73 ± 9.12	1.73 ± 0.80	**0.000**
Blood neutrophil percent (%)	54.80 ± 31.34	59.83 ± 9.22	**0.000**
Blood monocyte percent (%)	6.99 ± 4.27	6.21 ± 1.45	**0.007**
Serum total IgE (kU/l)	209.82 ± 287.30	199.04 ± 499.99	**0.002**
Blood lymphocyte percent (%)	32.93 ± 7.34	31.44 ± 8.64	0.070
Eosinophils exfoliated cells	1.56 ± 0.50	1.81 ± 0.40	**0.000**
Endoscope score(total)	6.82 ± 2.46	7.10 ± 2.85	0.487
Lund-Kennedy endoscopic score, E/M ratio*	2.26 ± 0.74	1.87 ± 0.96	**0.000**
Lund–Mackay CT score (total)	15.51 ± 6.33	14.31 ± 6.56	0.219
ECRSwNP: eosinophilic chronic rhinosinusitis with nasal polyps; SD: standard deviation; E/M: ethmoid versus mastoid.			
Analysis method: Mann-Whitney U test			

Comparison of profiles of nasal symptoms between eosinophilic and non-eosinophilic NP groups

A total of 286 patients completed the questionnaires, including148 eCRSwNP patients and 138 non-eCRSwNP patients. Loss of smell was the symptom with the most distinct difference between the two groups, and olfactory disorder was the unique symptomatic complaint that was significantly different between the two groups ($P = 0.000$). In addition, the VAS scores of nasal congestion, rhinorrhea, olfactory disorder, and head/facial pain did not significantly differ between these two groups. We further evaluated nasal congestion through rhinomanometry and found that unilateral or bilateral nasal resistance at either 75pa or 150pa was not significantly different between the two groups (see Additional Table 1). Moreover,

patients in the two groups complained about different primary symptoms. CRSwNPs patients were more likely to be puzzled by loss of smell (P = 0.002), and non-eCRSwNPs patients were more likely to be perplexed by nasal congestion (P = 0.001). The ratios of loss of smell were 57.4% and 39.1% in eCRSwNP and non-eCRSwNP groups, respectively. The ratios of nasal congestion were 38.5% and 58.0% in eosinophilic and non-eosinophilic NP groups, respectively. Details of the comparison of nasal symptoms are displayed in Table 2.

Table 2
Comparison of profiles of nasal symptoms between eCRSwNP and non-eCRSwNP patients.

Variables	**ECRSwNP (N = 148)**	**Non-eCRSwNP (N = 138)**	***P values***
VAS scores, median (IQR)			
Nasal congestion	5.70 ± 3.14	6.31 ± 2.93	0.113
Rhinorrhea	3.82 ± 3.11	3.27 ± 3.33	0.066
Olfactory disorders	6.50 ± 3.61	4.87 ± 3.65	**0.000**
Head/facial pain	2.34 ± 2.68	2.25 ± 2.71	0.323
Symptom with the highest severity, N (%)			
Nasal congestion	57 (38.5%)	80 (58.0%)	**0.001**
Rhinorrhea	22 (14.9%)	22 (15.9%)	0.801
Olfactory disorders	85 (57.4%)	54 (39.1%)	**0.002**
Head/facial pain	13 (8.78%)	14 (10.1%)	0.695
ECRSwNP: eosinophilic chronic rhinosinusitis with nasal polyps; VAS: visual analogue scale; IQR: Inter Quartile Range.			
Analysis method: Mann-Whitney U test			

To further determine the factors associated with olfactory function in CRSwNP, relevance analysis and logistic regression analysis were conducted based on between-group comparison analysis. Relevance analysis revealed that smell loss was related to disease duration (P = 0.026), blood eosinophilic percent (P = 0.01) and eosinophilic absolute counts (P = 0.001) in overall CRSwNP patients and blood neutrophilic percent (P = 0.031), blood lymphocyte percent (P = 0.014), and blood neutrophilic absolute counts (P = 0.013) in eCRSwNP patients. 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 total CRSwNP and non-eCRSwNP were significantly correlated with disease duration (P = 0.014, OR = 11.23; P = 0.008, OR = 1.21). These details are displayed in Table 3.

Table 3
Factors associated with olfactory function in CRWwNPs patients.

Variables	**Relevant analysis**		**Logistic analysis**		
	Coefficient	*P value*	OR	95% CI	*P values*
Total CRSwNP					
Disease duration	0.132	0.026	1.23	0.69–2.20	**0.014**
Blood Eosinophilic percent	0.152	0.01	2.09	0.94–4.67	**0.001**
Drinker	-0.197	0.011	6.63	1.49–29.66	**0.012**
ECRSwNP					
Blood Neutrophilic percent (%)	0.177	0.031	0.754	0.179–3.18	0.807
Blood Lymphocyte percent(%)	-0.201	0.014	2.20	0.72–6.70	0.228
Blood Neutrophil absolute counts(10^9 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	**0.008**
Drinker	-0.201	0.018	7.34	1.63–33.06	**0.009**
CRSwNP: chronic rhinosinusitis with nasal polyps; OR: Odds ratio; CI: Confidence interval.					
Analysis method: Mann-Whitney U test					

Using the ROC curves, we further explored the prominent predictive symptom that could be used to differentiate eCRSwNP and non-eCRSwNP. Among the four symptoms, olfactory dysfunction was the only valuable clinical marker for the predictive diagnosis of eCRSwNP. The details are displayed in Table 4, and the ROC curves are shown in Fig. 1 The AUC curves of four symptoms. 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 (P = 0.000).

Table 4
Diagnostic predictive values of parameters.

Parameters	AUC	95% CI	Cutoff value	Sensitivity	Specificity	*P* values
Olfactory disorders	0.624	0.559–0.689	5,75	0.662	0.594	**0.000**
Head/facial pain	0.563					0.067
Rhinorrhea	0.534					0.327
Nasal congestion	0.446					0.113

AUC: area under the curve; CI: Confidence interval.

In order to further examine the association of olfactory dysfunction with disease duration in eCRSwNP and non-eCRSwNP, we classified the patients into the following four groups based on the disease duration: less than 1 year, 1 to 5 years, 6 to 10 years, and more than 10 years. The results revealed significant differences between eCRSwNP and non-eCRSwNP patients in the three subgroups with disease duration of less than 10 years ($P = 0.013$, $P = 0.001$, $P = 0.011$). However, the difference between the two groups with the over ten-year duration was not significant ($P = 0.264$). Moreover, blood eosinophilic percent ($P = 0.001$, OR = 2.09) and eosinophilic absolute counts ($P = 0.001$, OR = 2.63) were correlated with loss of smell in the overall CRSwNP group. In addition, alcohol intake ($P = 0.009$, OR = 7.34) was another apparent influential factor for olfactory dysfunction in non-eCRSwNP patients. The details are displayed in Table 5.

Table 5
Comparison of nasal symptoms between eCRSwNP and non-eCRSwNP patients based on disease duration.

Variables	**eCRSwNP**	**Non-eCRSwNP**	***P values***
VAS scores, median (IQR)	**(N = 148)**	**(N = 138)**	
Duration: < 1 year	(N = 26)	(N = 30)	
Nasal congestion	4.50 ± 2.97	4.93 ± 3.42	*0.633*
Rhinorrhea	3.11 ± 2.83	2.49 ± 3.05	0.268
Olfactory disorders	6.07 ± 3.67	3.35 ± 3.44	**0.013**
Head/facial pain	2.75 ± 3.70	1.47 ± 1.96	0.071
Duration: 1–5 year	(N = 66)	(N = 44)	
Nasal congestion	5.48 ± 3.42	6.24 ± 2.98	0.386
Rhinorrhea	4.24 ± 3.24	3.17 ± 2.80	0.068
Olfactory disorders	6.76 ± 3.49	5.18 ± 3.35	**0.010**
Head/facial pain	2.40 ± 2.63	2.45 ± 2.72	0.864
Duration: 6–10 year	(N = 42)	(N = 44)	
Nasal congestion	6.54 ± 2.85	6.91 ± 2.35	0.782
Rhinorrhea	3.62 ± 3.18	3.79 ± 3.81	0.696
Olfactory disorders	6.52 ± 3.78	4.46 ± 3.57	**0.011**
Head/facial pain	2.47 ± 2.87	2.30 ± 3.07	0.266
Duration: > 10 year	(N = 14)	(N = 20)	
Nasal congestion	11.06 ± 17.37	7.19 ± 2.54	0.368
Rhinorrhea	3.76 ± 2.68	3.54 ± 3.61	0.546
Olfactory disorders	12.40 ± 25.47	7.34 ± 3.51	0.264
Head/facial pain	2.22 ± 3.15	2.89 ± 2.64	0.158

eCRSwNP: eosinophilic chronic rhinosinusitis with nasal polyps; VAS: visual analogue scale; IQR: Inter Quartile Ran.

Discussion

Olfactory disorder is an important clinical manifestation of CRSwNP. European and American scholars have statistically shown that about 14% and 10% of CRS patients have progressive olfactory dysfunction, respectively (1, 12). Although hyposmia 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 (13, 14). Studies have shown that the most common clinical symptom of eCRSwNP is olfactory disorders (15, 16), and ECRSwNP is usually resistant to drug therapy and surgical treatment and is prone to relapse after treatment. Therefore, eCRSwNP, an important category of refractory rhinosinusitis (17), has become the annoying bottleneck in the treatment of eosinophilic nasal polyps with functional endoscopic sinus surgery. To date, researchers have developed a variety of diagnostic approaches for eCRSwNP, such as blood routine tests, radiologic examinations, and tissue histopathology. Nevertheless, all these methods are invasive or need to wait for a long time to get the reports. Therefore, it is important to diagnose eCRSwNP using the first noticed primary complaints.

A total of 298 patients with CRSwNP were prospectively analyzed in our study, and the clinical characteristics of eCRSwNP and non-eCRSwNP were collected and described. Using the characteristics of the patients' clinical symptoms, we explored the initial diagnostic tendency. In our study, most CRSwNP patients were aged between forty and fifty years with a male dominance. Patients with eCRSwNP had a familiar history of asthma, and the findings are consistent with those in many previous studies (18–20). In addition, the CT manifestation of eCRSwNP was the centralization of polyps and edema mucosa in the ethmoid sinus and olfactory cleft region, and that of non-eCRSwNP was predominantly observed in the maxillary sinus. Our findings are similar to those in previous studies, which showed that the ethmoid and the maxillary sinus were predominantly involved in eCRSwNPs and non-eCRSwNPs, respectively (8, 21, 22). Notably, eCRSwNP patients complain mostly about olfactory dysfunction in the early days; non-eCRSwNP patients commonly present with nasal congestion, and olfactory sensation worsens over time. Therefore, olfactory dysfunction might be the most important clinical symptom in eCRSwNP and non-eCRSwNP patients.

Regarding physiology and pathophysiology of olfactory function, the first step in olfaction is to diffuse the odors to the olfactory epithelium located on the cribriform plate, the upper part of the nasal septum, and the middle and superior turbinate, which are called the olfactory area. Odors are dissolved in the mucus layer and then activate the olfactory receptors (14). Each odor can be recognized by an olfactory receptor through a complex code to help distinguish millions of odors. After processing, the olfactory information is integrated into the olfactory bulb and is then transmitted to the limbic system (sentiment), to the hippocampus (memory), and finally to the olfactory cortex (23). Olfactory disorders are associated with complicated fusions of a variety of triggers and involve not only physical obstructions of odors conduction, especially in the olfactory area (24), but also immunologic and chemical effects. Polyps in eCRSwNP are usually bilaterally involved in lesions, mostly in the ethmoid sinus, ostiomeatal complex, and olfactory area, where the olfactory epithelium is richly distributed. The polyps and edema of mucosa mechanically block the transmission of odors to the olfactory area (15, 25). The immunologic effect of eCRSwNP mainly involves type 2 inflammation due to nasal polyps or edema and is associated with production of IL-3, IL-5, IL-13, granulocyte-macrophage colony-stimulating factor, and eotaxin and up-regulation of adhesion molecules, thereby leading to ecclasis and degeneration of the olfactory epithelium until falling-down of olfactory function (26, 27). Moreover, neurotoxic mediators, known as eosinophilic derived neurotoxins, which are released by eosinophils, can damage the olfactory nerve (28),

impede the transmission of odors to the mucus and epithelium, and impair regeneration of neurons. As one of the four main proteins (major basic protein, eosinophil peroxidase, eosinophil-derived neurotoxin, and eosinophilic cationic protein [ECP]) in the eosinophils (29), ECP plays a devastating role by activating infiltration of the eosinophilic inflammatory cells in the neuroepithelium. *In vitro* studies have found that ECP gradually increases after exposure to pollen, and the increase is associated with the progression of hyposmia. Nevertheless, ECP can slower the frequency of nasal ciliary movement, even in the epithelial cells (30). All these complicated factors make the sensory receptor fragile to the pathologic stimuli (25, 27).

In our study, patients with eCRSwNP had more severe olfactory disorders than those with non-eCRSwNP. The number and severity of symptoms were significantly higher in eCRSwNP patients than in non-eCRSwNP patients. Using multiple regression analysis, we found that the high eosinophil level in the peripheral blood was an independent risk factor for olfactory dysfunction in CRSwNP patients. The higher the eosinophil level, the more severe the olfactory dysfunction. Haruna et al. reported that olfactory dysfunction was more significant when there were a large number of eosinophils in the ethmoid sinus mucosa than when there were a small number of eosinophils in the tissue (15). Mori et al. observed that eosinophilic CRS patients had more severe olfactory dysfunction than non-eosinophilic CRS patients, and smoking was a risk factor for olfactory dysfunction (31). Therefore, it has been believed that patients with eCRSwNP are more likely to suffer from 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. Therefore, if the VAS score of olfactory disorders is beyond 5.75, the patient might have 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 eosinophil levels, but not with the disease duration, in eCRSwNP patients. In contrast, olfactory disorders were related to the disease duration in non-eCRSwNP patients. The longer the duration, the more severe the hyposmia. Further, stratified analysis of the disease duration showed that when the disease duration was less than 10 years, patients with eCRSwNP had more apparent olfactory disorders, while patients with non-eCRSwNP mainly had nasal congestion. However, when the disease duration was more than 10 years, the symptoms of olfactory disorders became disturbing in both groups. These findings indicate that with the progression of the disease, olfactory dysfunction becomes more significant in non-eCRSwNP patients, probably because the reduplicate stimulation destroys the epithelium in the context of chronic inflammation (28, 30).

There are some limitations in the present study. First, the sample size was limited so that the disease duration could not be further subdivided, thus probably decreasing 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, the subjective judgment of VAS scores was used for the diagnosis of olfactory disorder; thus, other objective methods (such as the Sniffin' Sticks test) should be applied to increase the accuracy of diagnosis in future studies. Third, the

diagnostic criteria used in this study were based on the blood eosinophilia and were mainly used to distinguish eosinophilia-dominant from non-eosinophilia-dominant. Therefore, a relatively broad standard would more appropriately define the two types in clinical practice and help the diagnosis of olfactory disorders.

Conclusions

Olfactory disorder was the major nasal symptom that could be used to distinguish eCRSwNP and non-eCRSwNP. The accurate time boundary for better distinguishing between eCRSwNP and non-eCRSwNP would be our next step for further study. ECRSwNP patients were more prone to have olfactory dysfunction. Evaluation of nasal symptoms will help diagnose eCRSwNP and determine targeted subsequent clinical treatment strategies.

List Of Abbreviations

AUC: area under the curve; CI: confidence intervals; CRS: chronic rhinosinusitis; ECP: eosinophilic cationic protein; eCRSwNP: eosinophilic chronic rhinosinusitis with nasal polyps; IGF: insulin-like growth factor; IL: interleukin; OR: Odds ratios; ROC: receiver operating characteristic; VAS: visual analogue scale.

Declarations

Ethics approval and consent to participate: This study was approved by the Ethics Committee of Beijing Tongren Hospital, and written informed consent was obtained from patients before data collection.

Consent for publication: Consent of publication was obtained from all subjects.

Availability of data and materials: The datasets used and analyzed during the current study was available from the corresponding author on reasonable request

Competing interests: All authors declare no financial or commercial conflicts of interest.

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Authors' contributions: Yuan Zhang was the designer of the study. Yuan Zhang and Xiaodan Pan collected and analyzed the data, drafted and revised the manuscript. Chengshuo Wang and Luo Zhang designed the study, revised the paper, supervise the process and approve the final submission.

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Figures

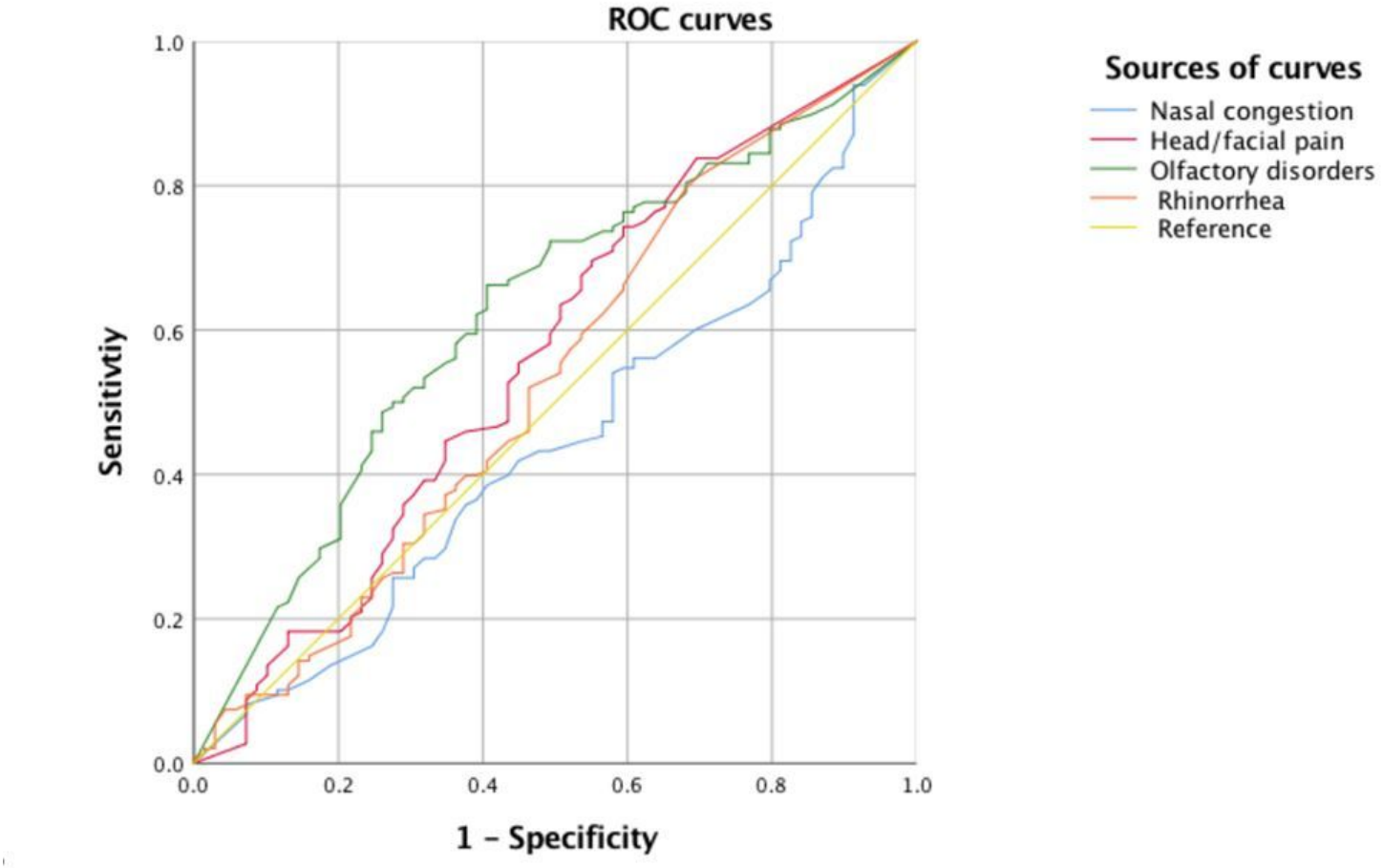

Figure 1

ROC curves of the four symptoms. The AUC of olfactory disorder (AUC = 0.642) was higher than those of other symptoms.

Supplementary Files

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