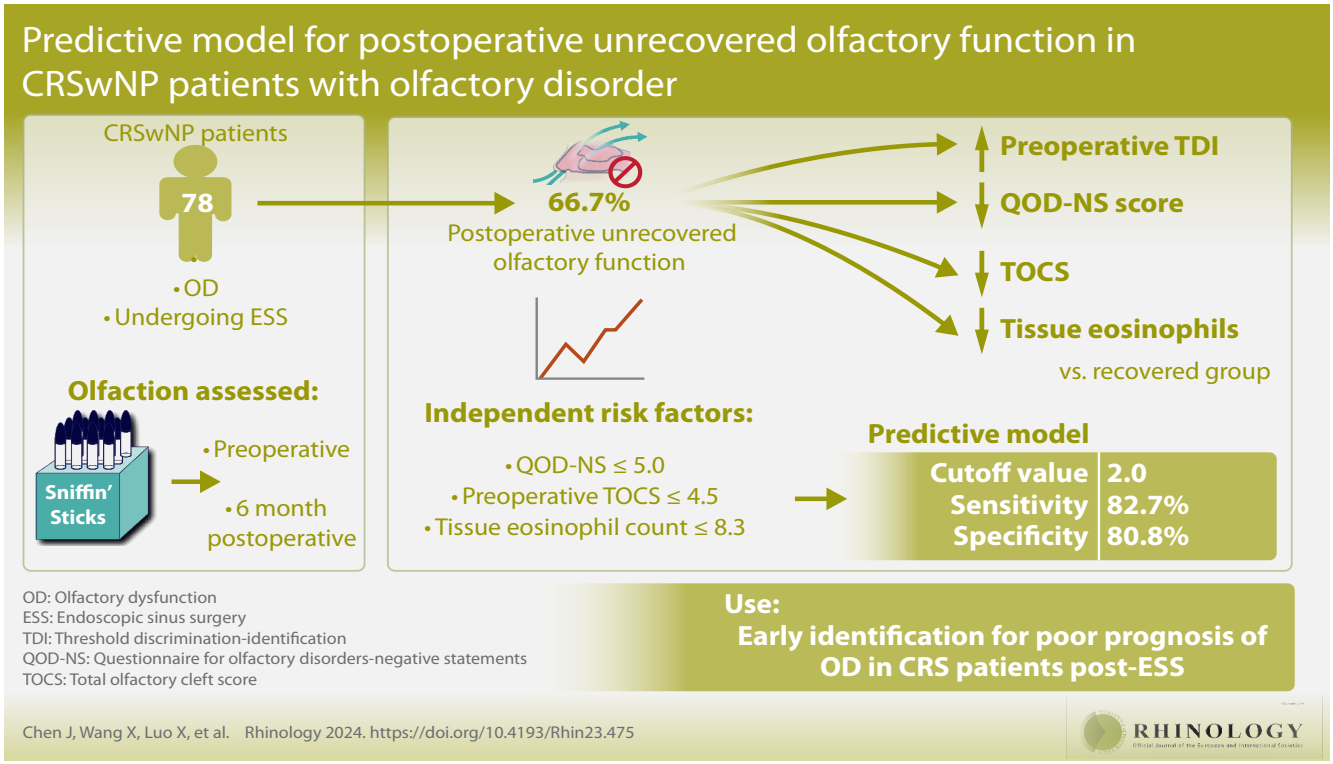
Predictive model for postoperative unrecovered olfactory function in CRSwNP patients with olfactory disorder

Jingyuan Chen[1,2,3,†], Xinyue Wang[1,2,3,†], Xin Luo[1,2,3,†], Feitong Jian[1], Wenhao Zhou[1,2,3], Zhenhao Xiao[1,2,3], Junhai Chen[1,2,3], Pengda Fang[1,2,3], Shuo Wu[1,2,4], Qiuli Liu[5], Xuekun Huang[1,2,3,4], Zhaohui Shi[1,2,4,*], Qintai Yang[1,2,3,4,*], Yana Zhang[1,2,3,*]

Rhinology 62: 6, 689 - 699, 2024
https://doi.org/10.4193/Rhin23.475



Abstract

Background: Olfactory disorder (OD) is a prevalent and challenging symptom in chronic rhinosinusitis with nasal polyps (CRSwNP). This study aims to investigate the risk factors and develop a predictive model for poor olfactory prognosis in CRSwNP patients with OD after endoscopic sinus surgery (ESS). **Method**: Seventy-eight CRSwNP patients with OD who underwent ESS were enrolled. Preoperative and 6-month-postoperative olfactory function were assessed using Sniffin' Sticks. Receiver operating characteristics (ROC) curves were constructed to set the cutoff points. Risk factors were determined by logistic models. A power analysis was conducted to evaluate the sample size. **Results**: Overall, 66.7% of CRSwNP patients had unrecovered olfaction after surgery. Patients with unrecovered olfaction displayed higher preoperative threshold-discrimination-identification (TDI) score, lower Questionnaire for Olfactory Disorders-Negative Statements (QOD-NS) score, lower total olfactory cleft score (TOCS), and fewer tissue eosinophils than those of the improved/recovered group. QOD-NS≤5.0, preoperative TOCS≤4.5 and tissue eosinophil count≤8.3 were independent risk factors for unrecovered olfaction. Based on these variables, a predictive model was developed. The area under the ROC curve for the model was 0.845, and the optimal cutoff value was 2.0 points, with a sensitivity of 82.7% and specificity of 80.8%. **Conclusions**: Low levels of QOD-NS score (preoperative), TOCS (preoperative) and tissue eosinophil count are independent risk factors for short-term unrecovered olfaction in CRS patients with OD postoperatively. The predictive model developed here is practical and convenient for the early identification of poor prognosis of OD, enabling early additional intervention.

Key words: olfactory disorder, chronic rhinosinusitis, endoscopic sinus surgery, eosinophil, corticosteroid

Introduction

Chronic rhinosinusitis (CRS) is a prevalent disease worldwide, affecting 8–14% of the population in China, the US and Europe [1]. Olfactory disorder (OD), as one of the main symptoms of CRS, affects approximately 60%~80% of patients with CRS, particularly those with chronic rhinosinusitis with nasal polyps (CRSwNP) [2]. OD is highly correlated with depressed mood, impaired taste, malnutrition and poor perception to danger, significantly impairing quality of life and productivity [3]. Additionally, OD is reported as an independent risk factor for increased mortality and is one of the most important symptoms that patients with CRSwNP desire to improve through medical and surgical treatment [4,5].

Poor prognosis of OD is associated with better preoperative olfaction, long disease course, previous sinus surgery, and superior turbinate eosinophilia [6-8]. Akiyama et al. found that patients with CRS who were female, <45 years old, and lacked olfactory cleft (OC) lesions achieved better olfaction improvement [9]. However, Pade et al. showed that neither age nor sex had a major effect on surgical outcomes in terms of olfaction and that patients with eosinophilia and high nasal polyps load may benefit from surgery in terms of olfactory recovery [10].

Endoscopic sinus surgery (ESS) is recommended a mainstay treatment for OD associated with CRSwNP [11]. However, previous studies reported that the rate of improved olfaction after ESS in CRSwNP varies from 17–50% [12-14], suggesting that the efficacy of ESS in improving olfactory function is far from satisfactory. Systemic and topical glucocorticoids (GCs) are recommended in clinical guidelines as an effective therapy for olfactory dysfunction secondary to CRSwNP due to their ability to reduce mucosal edema and scarring, as well as their anti-inflammatory effects [11]. However, repeated and long-term use of oral GCs has limited efficacy and increases the risk of adverse events [15,16]. Therefore, early identification of unrecovered olfaction in CRSwNP patients post-ESS is crucial for enabling additional interventions and precise early-stage treatments. The Sniffin' Sticks test and the University of Pennsylvania Smell Identification Test (UPSIT) are validated and reliable methods for detecting olfactory function but can be time-consuming and labor-intensive. Moreover, the Sniffin' Sticks test and UPSIT are not available in every hospital, specifically in non-tertiary hospitals. Thus, a convenient and practical predictive model for early evaluation of postoperative unrecovered olfaction is needed.

This study aimed to investigate the risk factors for unrecovered olfactory function in CRSwNP patients with OD post-ESS and to develop a predictive model for the poor prognosis of olfaction.

Materials and methods

Subjects

A prospective analysis was conducted from Jan. 2023 to Apr. 2024 at the Third Affiliated Hospital of Sun Yat-Sen University. The study was approved by the Third Affiliated Hospital of Sun Yat-Sen University Ethics Committee [RG2023-123-01]. Written informed consent was obtained from each subject. Figure S1 illustrates the experimental design. Inclusion and exclusion criteria for patients are provided in the Supplementary materials.

All patients with bilateral CRSwNP underwent ESS, with some also undergoing partial middle turbinate (MT) resection. The enrolled patients were followed up at 2 weeks, 1 month, 3 months and 6 months postoperatively. Besides, all patients who underwent ESS performed nasal irrigation daily and were administered intranasal budesonide spray (Rhinocort Aqua, AstraZeneca, Sweden), 128 μg twice daily for 3 months. Rescue oral steroids (methylprednisolone 12–16 mg daily for 2 weeks) were administered to patients with uncontrolled CRS according to EPOS 2020, with sufficient informed consent regarding side effects [17,18].

Olfactory testing and olfactory function evaluation

Olfactory function was assessed using "Sniffin' Sticks" (Burghart Instruments, Wedel, Germany) preoperatively and 6 months postoperatively. The olfactory functional diagnosis was obtained from the sum of scores for Threshold, Discrimination and Identification (TDI) score, ranging from 1–48 points with higher scores indicating superior olfactory performance. Scores ≤16 indicated anosmia, 16.25–30.5 indicated hyposmia, and ≥30.75 indicated normosmia [19]. In this study, OD was defined as TDI<30.75 which included patients with hyposmia and anosmia.

The postoperative change in olfactory function at 6 months post-surgery compared to the baseline was calculated. Patients with olfactory change reaching the minimal clinical important difference (MCID), defined as an increased TDI score ≥5.5 points, were classified as CRSwNP with improved/recovered olfaction [11]; others were classified as CRSwNP with unrecovered olfaction.

The Chinese version of the Questionnaire for Olfactory Disorders-Negative Statements (QOD-NS) was used to quantify patient perception of olfactory function [20].

The total olfactory cleft score (TOCS) was used to grade the OC opacification on CT as previously reported [21].

Detailed protocols of the Sniffin' Sticks test, QOD-NS and TOCS are provided in the Supplementary materials.

Histology assessment

Nasal polyp tissues from patients with CRSwNP were obtained during surgery. The pathology samples were fixed in 10% formalin, subjected to embedding and sectioned. Hematoxylin-Eosin (H&E) stained paraffin sections (4 μm) were observed under a microscope (Olympus CX33; Olympus Corporation, Japan). Ten random, nonoverlapping fields beneath the epithelial surface were selected for cell counting under a 400× high-power field for each specimen. Cell counting was performed in a blinded fashion regarding all clinical data. The intraclass correlation coefficient for tissue eosinophils count was 0.9 (95% confidence

Table 1. The demographic characteristics of CRSwNP patients with improved/recovered or unrecovered olfactory function following ESS.

Parameters	Improved/recovered (26, 33.3%)	Unrecovered (52, 66.7%)	P value
Age (y), mean ± SD	38.7 ±11.1	42.1 ±13.1	0.259
Gender, male, n (%)	18 (69.2%)	42 (80.8%)	0.254
BMI(Kg/m^2), median (IQR)	21.7 (19.2, 26.3)	23.5 (22.4, 25.9)	0.072
Atopy, n (%)	12 (46.2%)	25 (48.1%)	0.873
AR, n (%)	7 (26.9%)	16 (30.8%)	0.725
Asthma, n (%)	6 (23.1%)	5 (9.6%)	0.206
Smoker, n (%)	3 (11.5%)	9 (17.3%)	0.739
Serum total IgE (U/L), median (IQR)	72.5 (37.5, 179.8)	74.5 (42.3, 190.8)	0.758
Previous sinus surgery, n (%)	7 (26.9%)	11 (21.2%)	0.569
Deviated nasal septum, n (%)	7 (26.9%)	22 (42.3%)	0.185
Presence of OC lesions, n (%)	16 (61.5%)	35 (67.3%)	0.614
Partial MT resection, n (%)	16 (61.5%)	27 (51.9%)	0.421
Disease duration (y), median (IQR)	5.5 (2.0, 10.0)	3.0 (1.1, 9.0)	0.167
Preoperative status			
QOD-NS, median (IQR)	12.0 (6.0, 21.8)	3.5 (0.0, 12.0)	<0.001
Lund-Mackay score, median (IQR)	15.0 (12.8, 20.0)	15.0 (12.0, 19.0)	0.686
TOCS, median (IQR)	6.0 (5.0, 7.0)	4.0 (2.3, 5.0)	<0.001
TDI score, median (IQR)	11.0 (8.3, 17.8)	23.0 (17.8, 28.3)	<0.001
Postoperative status			
QOD-NS, median (IQR)	4.5 (0.0, 12.0)	4.0 (0.0, 8.8)	0.879
TDI score, median (IQR)	25.0 (20.0, 28.8)	22.5 (16.1, 25.5)	0.015
Postoperative oral corticosteroids use, n (%)	12 (46.2%)	14 (26.9%)	0.089

Abbreviations: ESS, endoscopic sinus surgery; CRSwNP, chronic rhinosinusitis with nasal polyps; SD, standard deviation; IQR, interquartile range; AR, allergic rhinitis; OC, olfactory cleft; MT, middle turbinate; QOD-NS, the questionnaire for olfactory disorders- negative statements; TOCS, total olfactory cleft score; TDI, threshold-discrimination-identification.

interval [CI]:0.8–0.9). For H&E-stained samples, eosinophils, neutrophils, plasma cells, lymphocytes, and total inflammatory cells were counted. The ratio (%) of each cell type was calculated for further analysis.

Statistical analysis

Statistical analyses were performed using SPSS 25.0 (IBM, Armonk, NY, USA). For continuous variables, the unpaired t-test was used to compare groups when the differences were normally distributed, and the Mann-Whitney U test was used to compare groups when the differences were not normally distributed. For categorical variables, the Chi-square test was used. Receiver operating characteristic (ROC) curves were generated to evaluate the optimal cutoff points for predictors of CRSwNP without olfactory recovery. The risk variables for CRSwNP without olfactory recovery were identified through stepwise univariate and multivariate logistic regressions. The predictive model was established according to previous reports [22-24]. Table S1 shows the power value for each parameter. All statistical tests were two-sided, with $P<0.05$ considered statistically significant. Detailed information is provided in the Supplementary materials.

Results

Clinical characteristics of CRSwNP patients with unrecovered olfactory function

Seventy-eight CRSwNP patients (60 male and 18 female) were eligible for this study. Overall, 52 patients (66.7%) had unrecovered olfaction (an increased TDI score<5.5 points), and 26 patients (33.3%) had improved/recovered olfaction (an increased TDI score≥5.5 points). The unrecovered rate of olfactory function (51.6%) was lower in anosmic patients compared to hyposmic patients (76.6%, $P<0.05$) (Figure S2). To distinguish the characteristics of CRSwNP patients with unrecovered olfaction, we first compared the demographic features between the olfactory function improved/recovered and unrecovered groups. Patients with unrecovered olfactory function displayed higher preoperative TDI score ($P<0.001$) and lower preoperative

Table 2. Inflammatory cells from tissue and blood in CRSwNP patients with improved/recovered or unrecovered olfactory function following ESS.

Parameters	Improved/recovered (26, 33.3%)	Unrecovered (52, 66.7%)	P value
Tissue assessment			
Total inflammatory cells count, median (IQR)	114.4 (82.5,220.3)	98.4 (59.5,154.7)	0.104
EOS count, median (IQR)	28.0 (7.7, 115.9)	5.9 (1.7, 39.9)	0.007
EOS%, median (IQR)	31.9 (6.5, 60.7)	6.6 (2.0, 39.5)	0.019
NEU count, median (IQR)	1.1 (0.2, 12.1)	0.2 (0.0, 2.0)	0.041
NEU%, median (IQR)	1.1 (0.2, 3.3)	0.3 (0.0, 2.5)	0.130
LYM count, median (IQR)	51.8 (32.4, 91.5)	55.5 (32.9, 87.9)	0.823
LYM%, median (IQR)	47.8 (26.7, 68.2)	72.5 (37.4, 85.8)	0.019
PC count, median (IQR)	8.8 (3.9, 27.8)	7.9 (3.4, 16.5)	0.307
PC%, median (IQR)	9.1 (2.9, 20.3)	8.6 (3.5, 14.5)	0.829
Preoperative peripheral blood assessment			
White blood cell count, median (IQR)	7.2 (5.2, 8.4)	6.6 (5.7, 7.8)	0.722
EOS count, median (IQR)	0.3 (0.1, 0.5)	0.3 (0.1, 0.4)	0.794
EOS%, median (IQR)	5.0 (1.2, 7.8)	3.4 (1.8, 5.8)	0.459
NEU count, median (IQR)	3.6 (2.6, 5.4)	3.6 (3.0, 4.5)	0.952
NEU%, median (IQR)	52.7 (50.3, 65.8)	54.6 (48.2, 60.8)	0.839
BASO count, median (IQR)	0.0 (0.0, 0.1)	0.0 (0.0, 0.1)	0.497
BASO%, median (IQR)	0.6 (0.3, 0.8)	0.5 (0.2, 0.7)	0.187
LYM count, median (IQR)	2.1 (1.5, 2.4)	2.1 (1.6, 2.7)	0.400
LYM%, median (IQR)	32.8 (22.6, 36.6)	32.7 (27.0, 37.9)	0.352
MONO count, median (IQR)	0.4 (0.3, 0.6)	0.5 (0.4, 0.6)	0.532
MONO%, median (IQR)	6.5 (5.2, 7.7)	7.0 (6.2, 8.4)	0.173

Abbreviations: ESS, endoscopic sinus surgery; CRSwNP, chronic rhinosinusitis with nasal polyps; IQR, interquartile range; EOS, eosinophil; NEU, neutrophil; LYM, lymphocyte; PC, plasma cell; IgE, immunoglobulin E; BASO, basophil; MONO, monocyte.

QOD-NS (P<0.001), TOCS (P<0.001), and postoperative TDI score (P=0.015) than the improved/recovered group (Table 1). However, the two groups did not significantly differ in other variables (Table 1) (P>0.050). Although the postoperative TDI score was lower in patients with unrecovered olfactory function compared to the improved/recovered group (P=0.015), the postoperative QOD-NS score was comparable between the two groups (P=0.879) (Table 1).

Inflammatory cells from tissue and peripheral blood in CRSwNP patients with unrecovered olfactory function

Since tissue and peripheral blood eosinophil levels are associated with olfactory dysfunction in CRS before surgery [25,26], we investigated whether eosinophils in nasal mucosa and peripheral blood would affect olfactory recovery. Contrary to our expectations, we found decreased counts (P=0.007) and percentages (P=0.019) of tissue eosinophils in the unrecovered olfaction group compared to the improved/recovered olfaction group. Likewise, a decreased number (P=0.041) of tissue neutrophils was observed in the unrecovered olfaction group relative to that in the improved/recovered olfaction group. However, the percentage (P=0.019) but not the count (P=0.823) of lymphocytes was higher in CRS patients with unrecovered olfaction compared to those with improved/recovered olfaction. Both groups were comparable in terms of total inflammatory cell count and the counts and ratios of plasma cells in the tissues. Interestingly, the counts and percentages of eosinophils, neutrophils, basophils, lymphocytes, and monocytes in peripheral blood were similar in both groups (Table 2). Additionally, 69.2% of patients in the improved/recovered olfaction group had type 2 inflammation (EOS>10/HPF) while 30.8% had non-type 2 inflammation. In contrast, 38.5% of patients in the unrecovered olfaction group had type 2 inflammation and 61.5% had non-type 2 inflammation (P=0.010) (Table S2). These results suggest that CRSwNP patients with type 2 inflammation may have a better postoperative olfactory prognosis than those with non-type 2 inflammation.

Cutoff value of variables for CRSwNP patients with unrecovered olfactory function

ROC analysis was performed to identify risk factors in CRSwNP

Table 3. Determination of cutoff value for continuous variables.

Variables	Cutoff Value	Sensitivity	Specificity	AUC	P value
Preoperative QOD-NS	5.0	59.6%	84.6%	0.730	0.001
Preoperative TOCS	4.5	65.4%	80.8%	0.749	<0.001
Preoperative TDI score	13.5	84.6%	73.1%	0.836	<0.001
Tissue EOS	8.3	61.5%	76.9%	0.686	0.008
Tissue EOS%	5.4	46.2%	84.6%	0.664	0.019
Tissue NEU	0.3	53.8%	69.2%	0.637	0.049
Tissue LYM%	67.8	55.8%	76.9%	0.662	0.020

Abbreviations: AUC, area under the curve; QOD-NS, negative statements portion of the questionnaire for olfactory disorders; TOCS, total olfactory cleft score; TDI, threshold-discrimination-identification; EOS, eosinophil; NEU, neutrophil; LYM, lymphocyte.

Table 4. Odds ratio of factors for CRSwNP with unrecovered olfactory function.

Variables	Univariate logistic regression		Multivariate logistic regression	
	OR (95%CI)	P value	OR (95%CI)	P value
Preoperative QOD-NS ≤5.0 *	8.1 (2.4-27.0)	0.001	7.5 (2.0-28.8)	0.003
Preoperative TOCS ≤4.5 *	8.9 (2.7-29.1)	<0.001	3.7 (1.0-13.6)	0.046
Tissue EOS ≤8.3 *	5.3 (1.8-15.5)	0.002	4.4 (1.2-16.0)	0.024
Tissue EOS% ≤5.4	4.7 (1.4-15.6)	0.011	-	-
Tissue NEU ≤ 0.3 *	3.2 (1.1-8.8)	0.027	0.6 (0.1-2.8)	0.558
Tissue LYM% ≥ 67.8	4.2 (1.5-12.2)	0.008	-	-

* The factor was included in the multiple logistic regression model. Each logistic regression was adjusted by prior surgery history, partial MT resection and postoperative oral steroids. Abbreviations: OR, odds ratio; CI, confidence interval; QOD-NS, negative statements portion of the questionnaire for olfactory disorders; TOCS, total olfactory cleft score; TDI, threshold-discrimination-identification; EOS, eosinophil; NEU, neutrophil; LYM, lymphocyte; MT, middle turbinate.

patients with unrecovered olfaction post-ESS, and the cutoff points for each variable that significantly differed between the groups were determined (Table 3). According to the ROC curve, preoperative QOD-NS≤5.0 (area under the ROC curve [AUC] 0.730), preoperative TOCS≤4.5 (AUC 0.749), preoperative TDI score≥13.5 (AUC 0.836), tissue eosinophil count≤8.3 (AUC 0.686), tissue eosinophil%≤5.4 (AUC 0.664), tissue neutrophil count≤0.3 (AUC 0.637) and tissue lymphocyte%≥67.8 (AUC 0.662) were optimal cutoff values for predicting unrecovered olfactory function in patients with CRS (P<0.050). These results implied that patients with higher TDI score and tissue lymphocyte ratio tended to have improved/recovered olfaction post-ESS, and lower values of preoperative QOD-NS, TOCS, tissue eosinophil count and tissue neutrophil count predicted poor outcomes of olfactory recovery.

Risk factors for CRSwNP patients with unrecovered olfactory function

Although the TDI score is considered the gold standard for evaluating olfactory function, it is time-consuming [6,13,27]. Thus, convenient parameters such as QOD-NS (preoperative), TOCS (preoperative), tissue eosinophil count, tissue eosinophil ratio, tissue neutrophil count and tissue lymphocyte ratio were analyzed to identify risk factors for unrecovered olfaction. The odds ratio (OR) value for these factors with the selected cutoff point is listed in Table 4. Setting the cutoff point at 5.0, preoperative QOD-NS had an OR of 8.1 (95%CI:2.4–27.0), while preoperative TOCS with the cutoff point at 4.5 had an OR of 8.9 (95%CI:2.7–29.1). Using 8.3 as the cutoff point, the OR value of tissue eosinophil count was 5.3 (95%CI:1.8–15.5), and the OR value of tissue eosinophil ratio was 4.7 (95%CI:1.4–15.6) with 5.4 as the cutoff point. When the cutoff point was at 0.3, the OR value of tissue neutrophil count was 3.2 (95%CI:1.1–8.8). The OR value of tissue lymphocyte ratio was 4.2 (95%CI:1.5–12.2), with 67.8 used as a cutoff value. Furthermore, all factors mentioned above were identified as important predictors in the univariate analysis. These risk factors identified by the univariate regression models were further introduced into a stepwise multivariate regression model to determine the independent risk factors for unrecovered olfaction of CRSwNP patients. Considering the high correla-

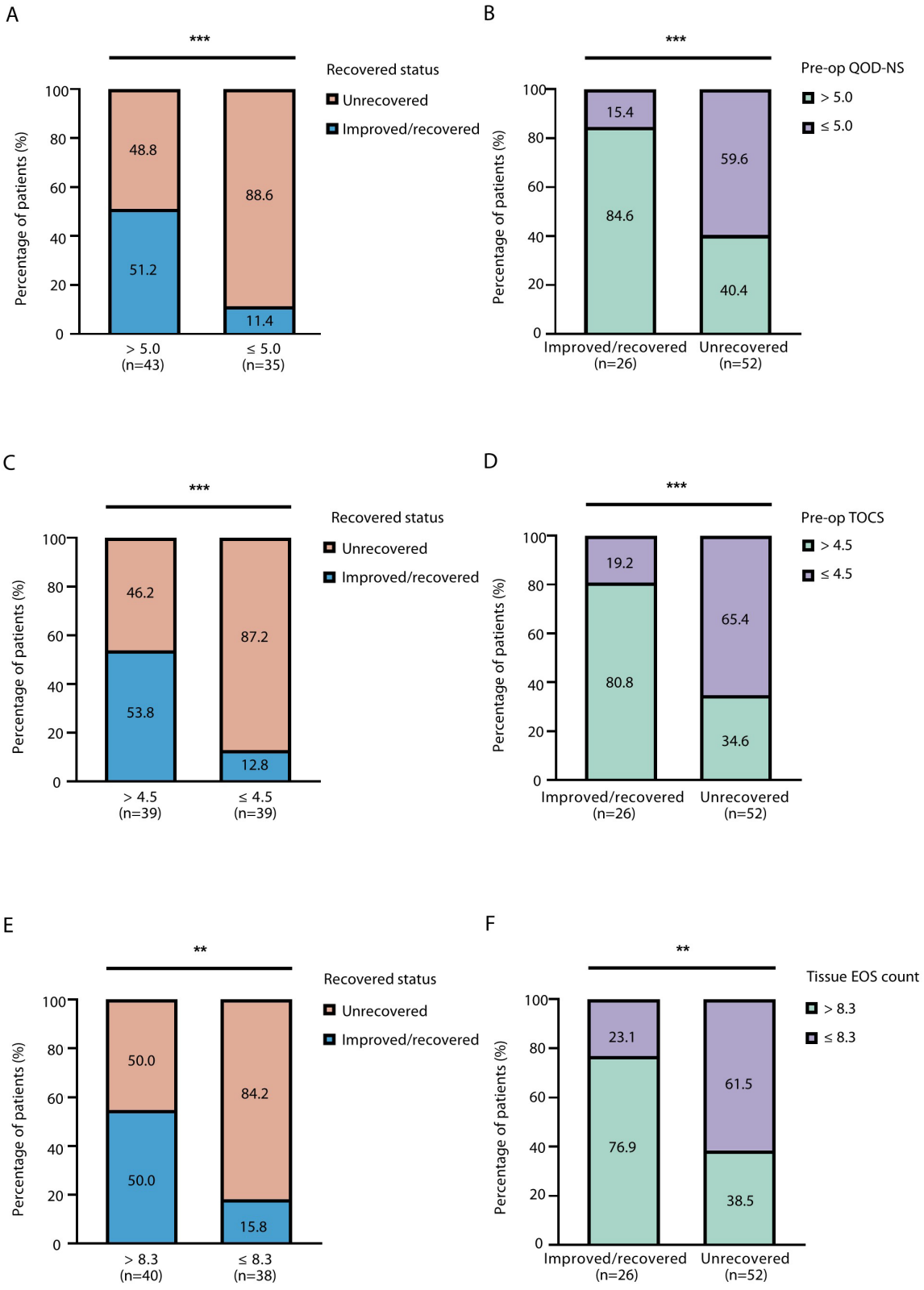


Figure 1. The percentages of CRSwNP patients with unrecovered olfactory function depend on different risk factors. The improved/recovered status in different levels of preoperative QOD-NS (A), preoperative TOCS (C) and tissue eosinophil count tissue (E); the preoperative QOD-NS (B), preoperative TOCS (D) and tissue eosinophil count (F) in different improved/recovered status groups. The numbers in the columns represent the percentage of patients in each group. **P < 0.01, ***P < 0.001. Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyps; Pre-op, preoperative; QOD-NS, negative statements portion of the questionnaire for olfactory disorders; TOCS, total olfactory cleft score; EOS, eosinophil.

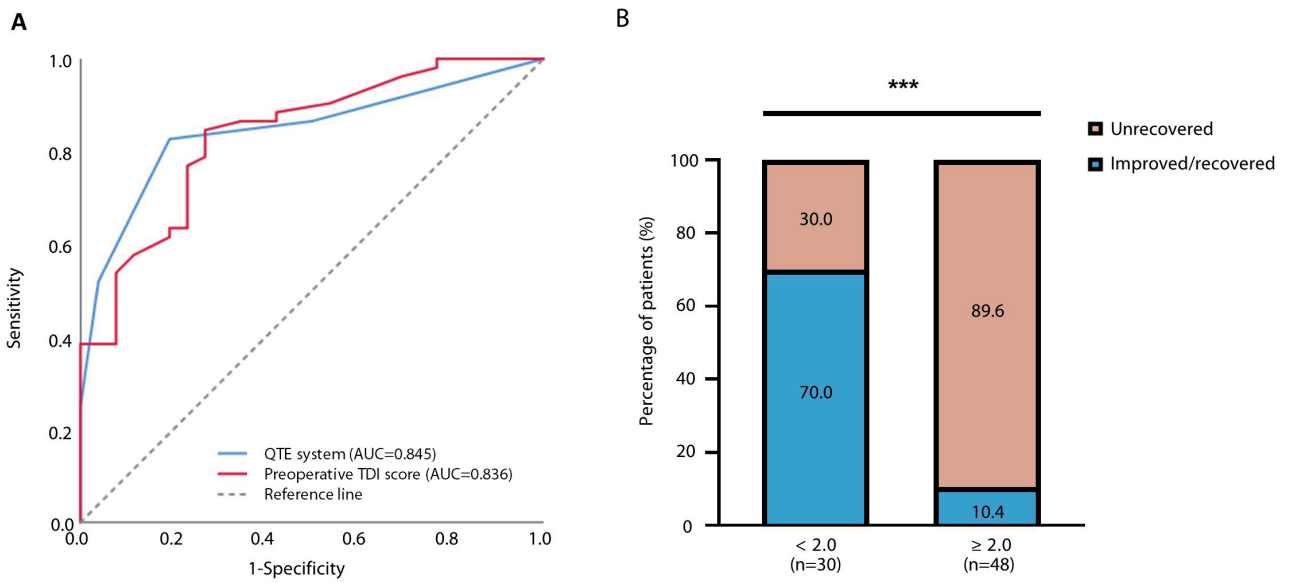


Figure 2. The predictive models for CRSwNP patients with unrecovered olfactory function after ESS. (A) ROC curves for QTE system and preoperative TDI score; (B) The rates of unrecovered olfaction and improved/recovered olfaction in different groups for the QTE system. The numbers in the columns represent the percentage of patients in each group. ***P < 0.001. Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyps; ROC, receiver operating characteristic; QTE, negative statements portion of the questionnaire for olfactory disorders, total olfactory cleft score and eosinophil; TDI, threshold-discrimination-identification; ESS, endoscopic sinus surgery.

tion between tissue eosinophil count and both tissue eosinophil ratio (r=0.9, P<0.001) and tissue lymphocyte ratio (r=–0.8, P<0.001), tissue eosinophil ratio and lymphocyte ratio were excluded from the multivariate analysis. After adjusted by prior surgery history, partial MT reduction and postoperative oral steroids, the multivariate analysis revealed that preoperative QOD-NS≤5.0 (β 2.0, adjusted OR 7.5, 95%CI:2.0–28.8, P=0.003), preoperative TOCS≤4.5 (β 1.3, adjusted OR 3.7, 95%CI:1.0–13.6, P=0.046) and tissue eosinophil count≤8.3 (β 1.8, adjusted OR 4.4, 95%CI:1.2–16.0, P=0.024) were independent risk factors for unrecovered olfactory function of CRSwNP patients (Table 4, Figure S3).

Relationship between unrecovered olfactory function and independent risk factors

The unrecovered rate of olfactory function (88.6%) was higher in patients with preoperative QOD-NS≤5.0 compared to those with preoperative QOD-NS>5.0 (48.8%, P<0.001) (Figure 1A). Additionally, 59.6% of patients in the unrecovered olfaction group had a preoperative QOD-NS≤5.0, whereas only 15.4% of those in the olfaction improved/recovered group had a preoperative QOD-NS>5.0 (P<0.001) (Figure 1B).

Patients with preoperative TOCS≤4.5 had a remarkedly higher unrecovered rate (87.2%) compared with those with a preoperative TOCS>4.5 (46.2%, P<0.001) (Figure 1C). While 65.4% of patients had a preoperative TOCS≤4.5 in the unrecovered group, 19.2% of patients in the improved/recovered group had a preoperative TOCS>4.5 (P<0.001) (Figure 1D).

The unrecovered rate of patients with tissue eosinophil count≤8.3 was higher (84.2%) than those with a tissue eosinophil count>8.3 (50.0%, P<0.010) (Figure 1E). Besides, 61.5% of patients had a tissue eosinophil count≤8.3 in the unrecovered group, while 23.1% of patients in the improved/recovered group had a tissue eosinophil count>8.3 (P<0.010) (Figure 1F).

These data suggest that improved/recovered olfaction is associated with increased preoperative QOD-NS, preoperative TOCS and tissue eosinophil count.

Establishment of a predictive model for unrecovered olfactory function of CRSwNP patients

Based on the method of a previous report [23,24], each risk factor (QOD-NS, TOCS and eosinophil count) was given a scoring point according to the β value (Table S3). A scoring system of the predictive model (QTE), with scores ranging from 0–4 (with 0=no risk and 4=high risk), was established to predict the unrecovered olfactory function in CRSwNP patients with OD post-ESS.

The AUC for the QTE system was 0.845, which was not significantly different from the AUC of the preoperative TDI score (Z=0.2, P=0.874) (Figure 2A), suggesting that the QTE system has a similar predictive capability to preoperative TDI score. Based on the Youden index, the optimal cutoff point of the QTE system was determined to be≥2.0, with a sensitivity and specificity of 82.7% and 80.8%, respectively. Employing the QTE system, 89.6% of the patients with score≥2.0 were identified as having unrecovered olfactory function post-ESS (P<0.001) (Figure 2B).

These data demonstrate that the QTE system possesses a capa-

bility comparable to the TDI score for predicting unrecovered olfaction in CRSwNP patients with OD who underwent ESS.

Discussion

The present study revealed that low levels of QOD-NS, TOCS and tissue eosinophil count are independent risk factors for unrecovered olfactory function in CRSwNP patients with OD after a 6-month-follow-up. We developed a predictive model for early identification of unrecovered postoperative olfaction in CRSwNP patients with OD.

In this study, 66.7% of CRSwNP patients who underwent ESS were found to have poor prognosis for OD following the 6-month follow-up. CRSwNP patients with higher preoperative TDI score had a greater risk of unrecovered olfactory function, consistent with the findings of previous research [6,13,27]. Besides, we observed that a preoperative TDI score≥13.5 exhibited the highly predictive capability for unrecovered olfaction (AUC 0.836; sensitivity 84.6%; specificity 73.1%). Although the Sniffin' Sticks test is the gold standard for olfaction evaluation, its practicality is limited in daily clinical practice due to time constraints, medical insurance policies and the economic status of patients, specifically in China. If preoperative TDI score was unavailable, our study demonstrated that decreased QOD-NS (≤5.0), TOCS (≤4.5), and tissue eosinophil count (≤8.3) are independent risk factors for postoperative unrecovered olfactory function of CRSwNP patients. Based on these risk factors, we established a predictive model named the QTE system. Previous studies have generated biometric predictive models to evaluate olfactory recovery post-ESS in CRSwNP patients. These models explained 70% of the observed variation in postoperative TDI scores and correctly classified 76% of patients who attained normal olfaction at 6 months [35]. No significant difference was observed between the ROC curves for the QTE system and the preoperative TDI score (Z=0.2, P=0.874), suggesting that they have similar predictive efficacies. Thus, the QTE system could promptly identify patients at risk of unrecovered olfactory function and facilitate the implementation of active and effective early-stage treatment measures, including olfactory training, and biologics.

Patients with eosinophilic chronic rhinosinusitis (ECRS) usually exhibit preoperative OD [29,30], likely due to more severe lesions and airflow obstruction in OC [31]. In this study, we demonstrated that patients with low tissue eosinophil count (≤8.3) may have a poor prognosis for postoperative olfaction since the olfactory loss of these patients was mainly caused by chronic inflammatory processes rather than conductive factors. For ECRS patients, ESS can be performed to remove the edematous mucosa and then significantly reduce the inflammatory burden including the local eosinophils levels, contributing to improved olfaction [32-34]. Previous reports indicated that the olfactory function of ECRS markedly improved at 3–6 months post-surgery, consistent with our findings [9,35]. However, only 33.3% of CRSwNP patients in our study had improved/recovered olfaction 6 months post-operation. Some research showed that tissue eosinophilia indicates unrecovered olfactory function post-ESS [7,34,36], possibly due to the different follow-up periods (3–24 months). Oka et al. found that olfactory dysfunction in ECRS showed transient improvement but deteriorated over time post-surgery (≥12 months post-surgery) [37], possibly due to the higher recurrence rate of ECRS [29,38]. In addition to the different follow-up times and recurrence status, differences in methods of olfactory function evaluation, definition of olfactory outcome and sites of obtained specimens also account for the inconsistent results. In addition to eosinophils, the level of degranulated eosinophil proteins such as galectin-10 and eosinophil-derived neurotoxin were highly associated with OD in CRS patients. Detecting these proteins may be more effective for reflecting the degree of eosinophilic inflammation and severity of OD. Thus, further research is warranted to explore the relationship between degranulated eosinophil proteins and olfactory dysfunction.

QOD-NS has been confirmed as a valid and reliable parameter for assessing olfaction-specific quality of life. A higher score reflects worse olfactory-specific quality of life and poorer olfactory function [20]. Our study showed that patients with low QOD-NS scores (≤5.0) have a higher risk of unrecovered olfaction, consistent with a previous finding that CRS patients with relatively better baseline olfaction may have worse olfactory outcomes post-surgery [39]. These patients often only have mild olfactory impairment, resulting in minimal alterations between preoperative and postoperative TDI score. Zhang et al. found that the disease course of self-reported smell loss in the recovered group was significantly shorter than in those with unrecovered olfactory function, indicating that long-term inflammation in the OC may lead to neurological necrosis [8]. Consequently, early detection and intervention are crucial, as these patients could benefit significantly from surgery.

TOCS reflects the extent of OC opacification and is correlated with objective measures of olfaction in patients with CRS (40). Recently, TOCS was found to be more sensitive in reflecting olfactory function than the Lund-Mackay score [41]. In this study, we found that patients with lower TOCS (≤4.5) may have limited olfaction improvement post-ESS. Patients with lower TOCS often have sensorineural but less conductive olfactory loss, making them less likely to benefit from the surgery. Kim et al. held a contradictory view that the recovery rate was much higher in patients with mild TOCS [21]. Another study demonstrated that patients with highly opacified anterior ethmoid benefited from ESS, which was consistent with our results [14]. This discrepancy may be due to the different definitions of recovered olfactory function.

Systemic GCs are one of the main treatments for CRS patients with OD [17]. Systemic GCs application may reduce mucosa edema and scarring as well as suppress inflammation post-ESS.

However, the duration of benefit from systemic GCs may be limited, and repeated use may lead to adverse events [15,16]. A randomized, double-blinded, placebo-controlled trial conducted by Wright and Agrawal showed that CRSwNP patients receiving perioperative oral GCs had significantly improved olfactory function compared with baseline levels at 2- and 4-weeks post-surgery. However, this therapeutic effect faded at 3 and 6 months [42]. Another multicentered, randomized, placebo-controlled clinical trial implied that administration of systemic GCs in CRSwNP patients post-ESS did not confer short-term or long-term benefits over those of topical steroid nasal spray alone with respect to smell scores [43]. In this study, the rate of patients receiving postoperative oral GCs was not observed to be significantly different between the olfaction improved/recovered and unrecovered group (P=0.089). The prescription of oral GCs depended on re-examining the condition at each follow-up visit, and the differing courses between the postoperative olfactory test and oral GCs treatment probably led to this result. Besides, the additional effects of oral GCs may have been masked by the strong effect of the surgery. Furthermore, long-term inflammation is believed to cause a functional shift in olfactory stem cell populations from neuroregeneration to immune defense and neuroepithelial remodeling, which is irreversible by oral GCs [44,45].

This study had some limitations. First, the cohort for this study was small. Thus, a multicenter clinical trial with a larger cohort is warranted in the future. Second, all the patients in this study were from South China; therefore, the generalizability of our predictive model needs to be validated in other populations. Third, the predictive model established based on QOD-NS, TOCS and tissue eosinophil count is designed for olfactory evaluation in CRSwNP patients with OD post-ESS and may not apply to OD patients before ESS. Fourth, we and others demonstrated that patients with lower TDI scores have a higher statistical probability to improved olfaction [6,46], which may lead to a bias. Since some patients have improved TDI but not uncovered olfaction. Predictive models for unrecovered olfaction should be studied in the future. Fifth, despite the improvement being larger in the improved/recovered group, the difference is only 2.5 points. The clinically relevant improvement should be further explored in a larger cohort.

Conclusion

Olfactory dysfunction is a very common and difficult-to-treat symptom of CRSwNP. Our study revealed that lower levels of preoperative QOD-NS, TOCS and tissue eosinophil count are independent risk factors for short-term unrecovered olfaction in CRSwNP patients with OD. The QTE system appears to be a useful and convenient predictive model for identifying CRSwNP patients at risk of uncovered olfactory function post-surgery. It should be helpful for early identification and prompt intervention (olfactory training, GCs and biological therapy) for CRSwNP patients with poor prognosis of olfaction.

Acknowledgement

We thank Yang laboratory members for constructive suggestions during our research.

Authors' contributions

Jingyuan Chen, Yana Zhang and Qintai Yang designed this study. Jingyuan Chen, Xinyue Wang, Feitong Jian, Wenhao Zhou, Xin Luo, Zhenhao Xiao, Junhai Chen, Pengda Fang, Xuekun Huang, and Qiuli Liu performed data collection and helped with the enrolment of participants. Shuo Wu and Zhaohui Shi performed the surgeries and helped with the sample collection. Jingyuan Chen and Xinyue Wang performed data analysis and drafted the manuscript. Yana Zhang and Qintai Yang did critical revision. All authors participated in scientific discussions and approved the final manuscript.

Funding

National Key R&D Program of China (2022YFC2504100); The National Natural Science Foundation of China (82271148, U20A20399, 82171114, 82371121); The General Program of Natural Science Foundation of Guangdong Province (2021A1515011764, 2022A1515011787, 2024A04J6570, 2024A1515010052); Science and Technology Projects in Guangzhou (2023A03J0209); Sun Yat-sen University Clinical Research 5010 Program (2019006); The Third Affiliated Hospital of Sun Yat-sen University "Five by Five" Project (2023ww601).

Conflicts of interest

The authors declare that they have no conflict of interest.

References

1. Shi JB, Fu QL, Zhang H, Cheng L, Wang YJ, Zhu DD, et al. Epidemiology of chronic rhinosinusitis: results from a cross-sectional survey in seven Chinese cities. Allergy. 2015;70(5):533-539.
2. Rombaux P, Huart C, Levie P, Cingi C, Hummel T. Olfaction in chronic rhinosinusitis. Curr Allergy Asthma Rep. 2016;16(5):41.
3. Croy I, Nordin S, Hummel T. Olfactory disorders and quality of life--an updated review. Chem Sens. 2014;39(3):185-194.
4. Mattos JL, Rudmik L, Schlosser RJ, Smith TL, Mace JC, Alt J, et al. Symptom importance, patient expectations, and satisfaction in chronic rhinosinusitis. Int Forum Allergy Rhinol. 2019;9(6):593-600.
5. Hummel T, Pinto JM, Wroblewski KE, Kern DW, Schumm LP, McClintock MK. Olfactory dysfunction predicts 5-year mortality in older adults. PLoS ONE. 2014;9(10):e107541.
6. Hintschich CA, Pade J, Petridis P, Hummel T. Presurgical olfactory function as an indicator of the outcome of functional endoscopic sinus surgery in chronic rhinosinusitis with nasal polyps. Eur Arch Otorhinolaryngol. 2022;279(12):5727-5733.
7. Wu D, Li Y, Bleier BS, Wei Y. Superior turbinate eosinophilia predicts olfactory decline in patients with chronic rhinosinusitis. Ann

Allergy, Asthma Immunol. 2020;125(3):304-10.e1.
8. Zhang W, Meng Y, Wang C, Cao F, Zhang L. Self-reported course of olfactory impairment determines outcome for successful surgical intervention in nasal polyps with anosmia. Acta Oto-Laryngologica. 2020;140(12):1021-1027.
9. Akiyama K, Samukawa Y, Hoshikawa H. Short-term outcomes of olfaction in patients with eosinophilic chronic rhinosinusitis after endoscopic sinus surgery and an assessment of prognostic factors. Int Forum Allergy Rhinol. 2019;10(2):208-216.
10. Pade J, Hummel T. Olfactory function following nasal surgery. Laryngoscope. 2009;118(7):1260-1264.
11. Whitcroft KL, Altundag A, Balungwe P, et al. Position paper on olfactory dysfunction: 2023. Rhinology. 2023;61(31):1-110.
12. Haxel BR. Recovery of olfaction after sinus surgery for chronic rhinosinusitis: A review. Laryngoscope. 2019;129(5):1053-1059.
13. Haxel BR, Fischer L, Pade J, Reden J, Hummel T. Nasal polyp load determines the recovery of olfaction after surgery for chronic rhinosinusitis. Rhinology. 2022;60(2):102-108.
14. Kim BG, Kang JM, Shin JH, Choi HN, Jung YH, Park SY. Do sinus computed tomography findings predict olfactory dysfunction and its postoperative recovery in chronic rhinosinusitis patients? Am J Rhinol Allergy. 2015;29(1):69-76.
15. Poetker DM, Jakubowski LA, Lal D, Hwang PH, Wright ED, Smith TL. Oral corticosteroids in the management of adult chronic rhinosinusitis with and without nasal polyps: an evidence-based review with recommendations. Int Forum Allergy Rhinol. 2013;3(2):104-120.
16. Van Zele T, Gevaert P, Holtappels G, et al. Oral steroids and doxycycline: two different approaches to treat nasal polyps. J Allergy Clin Immunol. 2010;125(5):1069-1076.e4.
17. Fokkens W, Lund V, Hopkins C, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology. 2020;58:1-464.
18. Subspecialty Group of Rhinology, Editorial Board of Chinese Journal of Otorhinolaryngology Head and Neck Surgery, Subspecialty Group of Rhinology, Society of Otorhinolaryngology Head and Neck Surgery, Chinese Medical Association. [Chinese guidelines for diagnosis and treatment of chronic rhinosinusitis (2018)]. Zhonghua er bi yan hou tou jing wai ke za zhi. 2019;54(2):81-100.
19. Oleszkiewicz A, Schriever VA, Croy I, Hähner A, Hummel T. Updated Sniffin' Sticks normative data based on an extended sample of 9139 subjects. Eur Arch Otorhinolaryngol. 2018;276(3):719-728.
20. Yuan F, Wu D, Wei Y. Predictive significance of the questionnaire of olfactory disorders-negative statements for olfactory loss in patients with chronic rhinosinusitis. Eur Arch Otorhinolaryngol. 2022;279(11):5253–5262.
21. Kim DW, Kim J-Y, Jeon S-Y. The status of the olfactory cleft may predict postoperative olfactory function in chronic rhinosinusitis with nasal polyposis. Am J Rhinol Allergy. 2011;25(2):e90-e94.
22. Tao X, Chen F, Sun Y, et al. Prediction models for postoperative uncontrolled chronic rhinosinusitis in daily practice. Laryngoscope. 2018;128(12):2673-2680.
23. Padilla-Galo A, Olveira C, Fernández de Rota-Garcia L, et al. Factors associated with bronchiectasis in patients with uncontrolled asthma; the NOPES score: a study in 398 patients. Respir Res. 2018;19(1):43.
24. Li F, Wang X, Shen S, et al. Risk factors associated with comorbid asthma in patients with chronic rhinosinusitis with nasal polyps: a cross-sectional study. BMC Pulm Med. 2022;22(1):338.
25. Lavin J, Min JY, Lidder AK, et al. Superior turbinate eosinophilia correlates with olfactory deficit in chronic rhinosinusitis patients. Laryngoscope. 2017;127(10):2210-2218.
26. Wu D, Liu Z, Bleier BS, Huang X, Hong J. Olfactory cleft mucus eosinophil-derived neurotoxin better reflects olfactory loss than blood eosinophil counts in patients with chronic rhinosinusitis. Int Forum Allergy Rhinol. 2023;13(12):2144-55.
27. Kohli P, Naik AN, Farhood Z, et al. Olfactory outcomes after endoscopic sinus surgery for chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2016;155(6):936-948.
28. Katotomichelakis M, Gouveris H, Tripsianis G, Simopoulou M, Papathanassiou J, Danielides V. Biometric predictive models for the evaluation of olfactory recovery after endoscopic sinus surgery in patients with nasal polyposis. Am J Rhinol Allergy. 2010;24(4):276-280.
29. Lou H, Meng Y, Piao Y, et al. Cellular phenotyping of chronic rhinosinusitis with nasal polyps. Rhinology. 2016;54(2):150-159.
30. Takeno S, Hirakawa K, Ishino T. Pathological mechanisms and clinical features of eosinophilic chronic rhinosinusitis in the Japanese population. Allergol Int. 2010;59(3):247-256.
31. Mori E, Matsuwaki Y, Mitsuyama C, Okushi T, Nakajima T, Moriyama H. Risk factors for olfactory dysfunction in chronic rhinosinusitis. Auris Nasus Larynx. 2013;40(5):465-469.
32. Yancey KL, Li P, Huang L-C, et al. Longitudinal stability of chronic rhinosinusitis endotypes. Clin Exp Allergy. 2019;49(12):1637-1640.
33. Jonstam K, Alsharif S, Bogaert S, et al. Extent of inflammation in severe nasal polyposis and effect of sinus surgery on inflammation. Allergy. 2021;76(3):933-936.
34. Zhang Z, Liu J, Xie L, Cao W, Ma F, Zhang Y. Tissue eosinophils and mucous inflammatory cytokines for the evaluation of olfactory recovery after endoscopic sinus surgery in patients with nasal polyposis. Am J Otolaryngol. 2022;43(5):103561.
35. Haruna S, Otori N, Moriyama H, Nakanishi M. Olfactory dysfunction in sinusitis with infiltration of numerous activated eosinophils. Auris Nasus Larynx. 2006;33(1):23-30.
36. Kashiwagi T, Tsunemi Y, Akutsu M, Nakajima I, Haruna S. Postoperative evaluation of olfactory dysfunction in eosinophilic chronic rhinosinusitis – comparison of histopathological and clinical findings. Acta Oto-Laryngol. 2019;139(10):881-889.
37. Oka H, Tsuzuki K, Takebayashi H, Kojima Y, Daimon T, Sakagami M. Olfactory changes after endoscopic sinus surgery in patients with chronic rhinosinusitis. Auris Nasus Larynx. 2013;40(5):452-457.
38. Tokunaga T, Sakashita M, Haruna T, et al. Novel scoring system and algorithm for classifying chronic rhinosinusitis: the JESREC Study. Allergy. 2015;70(8):995-1003.
39. AlBader A, Levine CG, Casiano RR. Does endoscopic sinus surgery improve olfaction in nasal polyposis? Laryngoscope. 2017;127(10):2203-2204.
40. Kohli P, Schlosser RJ, Storck K, Soler ZM. Olfactory cleft computed tomography analysis and olfaction in chronic rhinosinusitis. Am J Rhinol Allergy. 2016;30(6):402-406.
41. Soler ZM, Pallanch JF, Sansoni ER, et al. Volumetric computed tomography analysis of the olfactory cleft in patients with chronic rhinosinusitis. Int Forum Allergy Rhinol. 2015;5(9):846-854.
42. Wright ED, Agrawal S. Impact of perioperative systemic steroids on surgical outcomes in patients with chronic rhinosinusitis with polyposis: evaluation with the novel perioperative sinus endoscopy (POSE) scoring system. Laryngoscope. 2009;117(S115):1-28.
43. Mueller SK, Wendler O, Mayr S, al. Effect of postoperative systemic prednisolone on short-term and long-term outcomes in chronic rhinosinusitis with nasal polyps: A multi-centered randomized clinical trial. Front Immunol. 2023;14:1075066.
44. Chen M, Reed RR, Lane AP. Chronic inflammation directs an olfactory stem cell functional switch from neuroregeneration to immune defense. Cell Stem Cell. 2019;25(4):501-13.e5.
45. Yee KK, Pribitkin EA, Cowart BJ, et al. Neuropathology of the olfactory mucosa in chronic rhinosinusitis. Am J Rhinol Allergy. 2010;24(2):110-120.
46. Hernandez AK, Wendler O, Mayr S, Iro H, Hummel T, Mueller SK. Predictors of olfactory improvement after endoscopic sinus surgery in chronic rhinosinusitis with nasal polyps. J Laryngol Otol. 2023 May;137(5):524–531.

Yana Zhang, M.D., Ph.D.
Department of Otolaryngology-Head and Neck Surgery
The Third Affiliated Hospital of Sun Yat--Sen University
No. 600 Tianhe Road
Guangdong, Guangzhou 510630
China

Tel: +86-20-85253046
E-mail: zhangyn95@mail.sysu.edu.cn

Qintai Yang, M.D., Ph.D.
Department of Otolaryngology-Head and Neck Surgery
The Third Affiliated Hospital of Sun Yat--Sen University
No. 600 Tianhe Road
Guangdong, Guangzhou 510630
China

Tel: +86-20-85253046
E-mail: yangqint@mail.sysu.edu.cn

Zhaohui Shi, M.D., Ph.D.
Department of Otolaryngology-Head and Neck Surgery
The Third Affiliated Hospital of Sun Yat--Sen University
No. 600 Tianhe Road
Guangdong, Guangzhou 510630
China

Tel: +86-20-85253046
E-mail: shizhh35@mail.sysu.edu.cn

Jingyuan Chen[1,2,3,†], Xinyue Wang[1,2,3,†], Xin Luo[1,2,3,†], Feitong Jian[1], Wenhao Zhou[1,2,3], Zhenhao Xiao[1,2,3], Junhai Chen[1,2,3], Pengda Fang[1,2,3], Shuo Wu[1,2,4], Qiuli Liu[5], Xuekun Huang[1,2,3,4], Zhaohui Shi[1,2,4,*], Qintai Yang[1,2,3,4,*], Yana Zhang[1,2,3,*]

[1] Department of Otolaryngology-Head and Neck Surgery, The Third Affiliated Hospital of Sun Yat-sen University, Tianhe District, Guangzhou, China

[2] Department of Allergy, The Third Affiliated Hospital of Sun Yat-sen University, Tianhe District, Guangzhou, China

[3] Key Laboratory of Airway Inflammatory Disease Research and Innovative Technology Translation, Guangzhou, China

[4] Naso-Orbital-Maxilla and Skull Base Center, The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China

[5] The Biotherapy Center, The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China

Rhinology 62: 6, 689 - 699, 2024
https://doi.org/10.4193/Rhin23.475

Received for publication:
January 4, 2024
Accepted: August 28, 2024

† contributed equally
* contributed equally to design and supervision

Assocociate Editor:
Sietze Reitsma

This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

Subjects

A prospective analysis was performed from Jan. 2023 to Apr. 2024 in the Third Affiliated Hospital of Sun Yat-Sen University. Patients diagnosed with CRSwNP based on the current European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS 2020) and confirmed as having OD by Sniffin' Sticks were enrolled [1]. The atopic status was evaluated with a skin prick test using a standard panel of aeroallergens and/or ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden). Allergic rhinitis (AR) was diagnosed based on the concordance between a typical history of allergic symptoms and positive atopy test [2]. Asthma was diagnosed based on Global Initiative for Asthma guideline [3]. The patients treated with systemic GCs within 1 month before surgery and patients receiving biologics, antileukotriene Montelukast, antigen immunotherapy, immunosuppressants, or antineoplastic drug therapy were also excluded. There was no washout period for topical steroids and antibiotics in the study. Patients with cystic fibrosis, fungal rhinosinusitis, antrochoanal polyps, and upper respiratory airway infections within perioperative period and patients with normal olfactory function preoperatively were excluded in the current study.

Olfactory testing

Olfactory function was quantified preoperatively and 6 months postoperatively by using an established clinical test ("Sniffin' Sticks", Burghart Instruments, Wedel, Germany), which evaluated three sensory dimensions of odors comprising olfactory threshold, odor discrimination and odor identification. The threshold test was performed using dilutions of n-butanol in a single-staircase, triple-forced choice procedure. The discrimination test used triplets of pens presented in random order with two containing the same odorant and the third a different odorant. The identification test utilized 16 odorants presented at suprathreshold intensity using multiple-choice procedure. All subjects were blindfolded to avoid visual identification of odorant-containing pens. The olfactory functional diagnosis was obtained from the sum of scores in three tests mentioned above, named as Threshold, Discrimination and Identification (TDI) score, which ranged from 1 to 48 points with higher scores indicating superior olfactory performance. Of 16 or less indicated anosmia, values between 16.25 and 30.5 indicated hyposmia, and values of 30.75 and more indicated normosmia. In this study, we defined OD as TDI<30.75 which included patients with hyposmia and anosmia [4].

Patient-reported olfactory function

The patient-reported olfactory assessment was performed preoperatively and postoperatively before Sniffin' Sticks test using the Chinese version of Questionnaire for Olfactory Disorders-Negative Statements (QOD-NS) preoperatively in order to quantify patient perception of olfactory function [5,6]. The QOD-NS is a validated, olfactory specific QOL survey that consists of 17 discrete survey items summarized using Likert score responses from 0="disagree" to 3="agree" (score range:0–51) with higher scores indicating worse olfactory impairment [6,7].

Evaluation of olfactory cleft by CT imaging

The preoperative CT images (2.5 mm thickness) were evaluated in the axial and coronal planes without contrast enhancement. Physicians who analyzed the CT scan results were blind to all the grouping information.

The borders of the olfactory cleft in CT were defined as follows: anterior (anterior attachment of the middle turbinate); posterior (anterior wall of the sphenoid sinus); medial (nasal septum); and lateral borders (middle and superior turbinate). The superior border was the skull base, and the inferior border was the inferior portion of the middle turbinate. The olfactory cleft was divided into anterior and posterior parts by the anterior end of the superior turbinate. The anterior and posterior olfactory cleft opacifications were graded separately on a scale of 0-4 by the ratio of the opacified area to the whole area of the olfactory cleft, with 0 (no opacification), 1 (0-25%), 2 (25-50%), 3 (50-75%) and 4 (>75%). The total olfactory cleft score (TOCS), which was calculated as the sum of the anterior olfactory cleft score and the posterior olfactory cleft score, ranged from 0 to 8 [8].

Statistical analysis

Statistical analysis was performed by SPSS 25.0 (IBM, Armonk, NY, USA). Continuous variables were presented as mean and standard deviation when normally distributed or as median and interquartile range when not normally distributed. Categorical variables were presented as frequencies and percentages. For continuous variables, the unpaired t test was used for comparison in two groups when the differences were normally distributed, and the Mann-Whitney U test for comparison in two groups when the differences were not normally distributed. For categorical variables, the Chi-square test was used for comparison in groups. Receiver operating characteristic (ROC) curves were generated to evaluate the optimal cutoff points for predictors for CRSwNP without olfactory recovery. The area under the curve (AUC) for each predictor was calculated. The cutoff points for continuous variables were decided according to the maximal Youden index. In order to establish the predictive model and facilitate the calculation of scores, the quantitative variables obtained were converted into dichotomic variables according to

the cutoff points for each variable [9]. The risk variables identified by univariate logistic regressions were conducted into multiple logistic regression models by the methods of stepwise regression. Multivariate logistic regression analysis was used to assess the relationship between risk variables and CRSwNP without olfactory recovery. The partial regression coefficient (β), odds ratio (OR) and 95% CI were calculated for each variable. The risk variable of smallest β was counted as a reference, and given a value of "1". The score of other variables was obtained by dividing their β value by β of the reference variable to form a prediction model [10,11]. The sample size for the logistic regression models was determined on a minimum of about 10 events per explanatory variable [9,12]. Power analysis was conducted using PASS (version 15) to calculate sample size needed in the current study. All statistical tests were two-sided, and a P value < 0.05 was considered statistically significant.

Table S1. Power value for each parameter in the study.

Variables	N1	N2	P1	P2	Power
Preoperative QOD-NS ≤5.0	26	52	15.4%	59.6%	1.0
Preoperative TOCS ≤4.5	26	52	19.2%	65.4%	1.0
Tissue EOS ≤8.3	26	52	23.1%	61.5%	0.9
Tissue NEU ≤ 0.3	26	52	26.9%	53.8%	0.7

Power is calculated using PASS (version 15) with a two-tailed α value of 0.05. N1 indicates improved/recovered group, N2 indicates unrecovered group, P1 and P2 indicates the relative proportion of variables in each group.

Table S2. The endotype characteristics between CRSwNP with improved/recovered and unrecovered olfactory function.

Parameters	Improved/recovered (26, 33.3%)	Unrecovered (52, 66.7%)	P value
Type 2 CRSwNP, n (%)	18 (69.2%)	20 (38.5%)	0.010
Non-Type 2 CRSwNP, n (%)	8 (30.8%)	32 (61.5%)	

Type 2 CRSwNP is determined by the number of eosinophils (>10/HPF, 400×) according to EPOS 2020. Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyps; HPF, high power field.

Table S3. Scoring system of predictive model for CRSwNP patients with uncovered olfactory function.

Factors	Points
Preoperative QOD-NS	
≤5.0	2.0
>5.0	0.0
Preoperative TOCS	
≤4.5	1.0
>4.5	0.0
Tissue EOS count	
≤8.3	1.0
>8.3	0.0

Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyps; QOD-NS, negative statements portion of the questionnaire for olfactory disorders; TOCS, total olfactory cleft score; EOS, eosinophil.

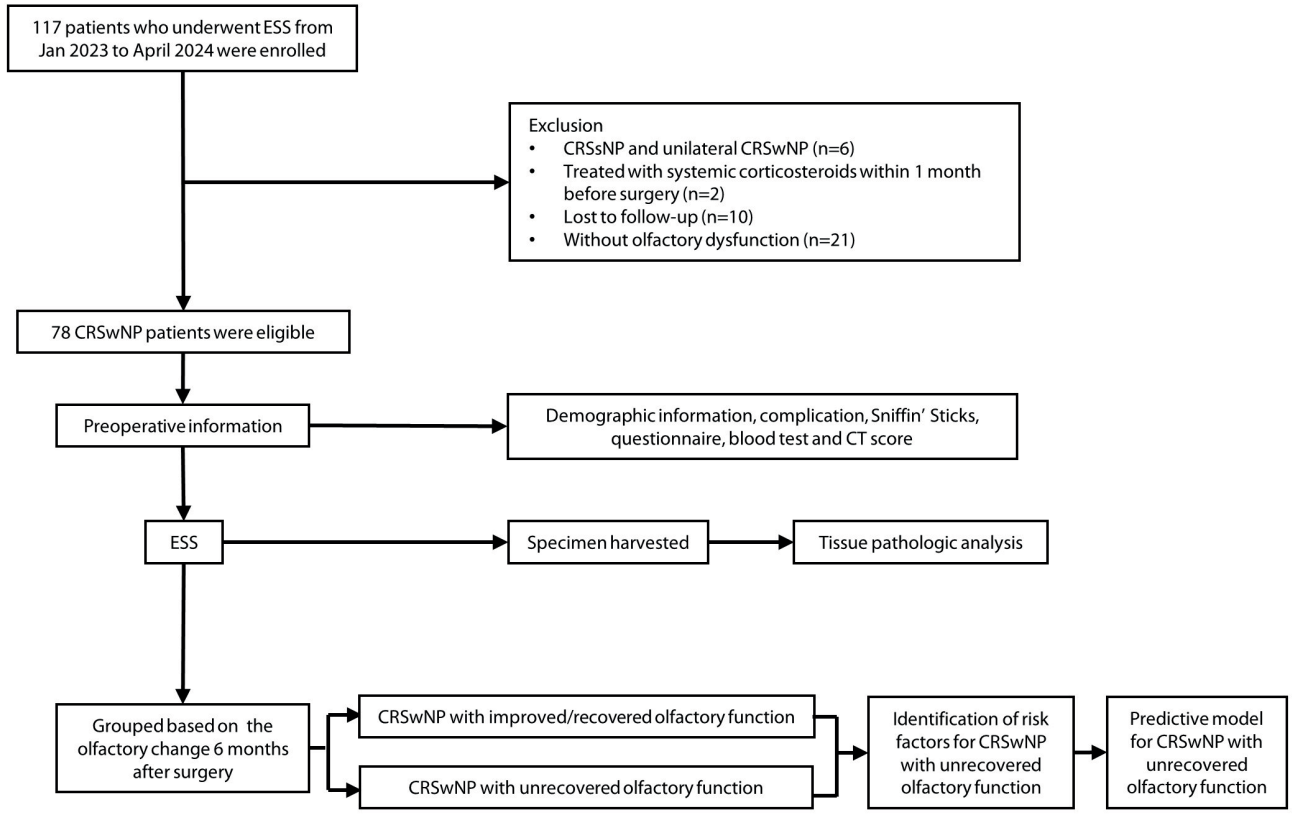


Figure S1. Flow diagram of the study design. Abbreviations: ESS, endoscopic sinus surgery; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; CT, computed tomography.

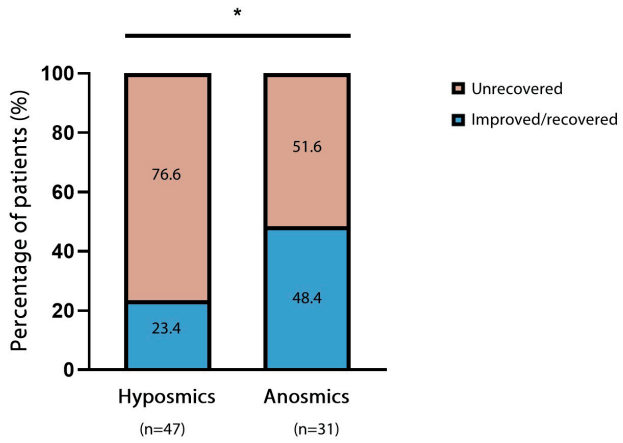


Figure S2. The postoperative unrecovered status of hyposmic and anosmic CRSwNP patients. The numbers in the columns represent the percentage of patients in each group. *P < 0.05. Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyps; TDI, threshold-discrimination-identification.

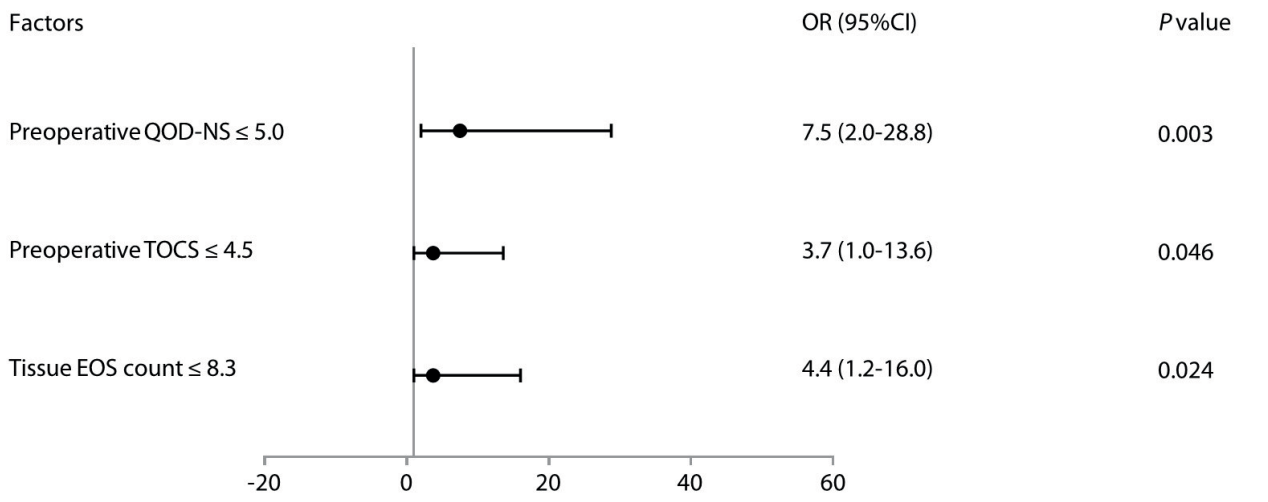


Figure S3. Risk factors associated with unrecovered olfaction in CRSwNP patients in the predictive model. Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyps; OR, odds ratio; CI, confidence interval; QOD-NS, negative statements portion of the questionnaire for olfactory disorders; TOCS, total olfactory cleft score; EOS, eosinophil.

References

1. Fokkens WJ, Lund VJ, Hopkins C, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology. 2020 Feb 20;58(Suppl S29):1-464.
2. Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. J Allergy Clin Immunol. 1998 Oct;102(4 Pt 1):558–562.
3. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy. 2008 Apr;63 Suppl 86:8–160.
4. Oleszkiewicz A, Schriever VA, Croy I, Hähner A, Hummel T. Updated Sniffin' Sticks normative data based on an extended sample of 9139 subjects. Eur Arch Otorhinolaryngol. 2019 Mar;276(3):719-728.
5. Yang D, Wang J, Ni D, Liu J, Wang X. Reliability and validity of the Chinese version of the questionnaire of olfactory disorders (QOD) when used with patients having olfactory dysfunction. Eur Arch Otorhinolaryngol. 2016 Oct;273(10):3255–61.
6. Yuan F, Wu D, Wei Y. Predictive significance of the questionnaire of olfactory disorders-negative statements for olfactory loss in patients with chronic rhinosinusitis. Eur Arch Otorhinolaryngol. 2022 Nov;279(11):5253–62.
7. Mattos JL, Schlosser RJ, Mace JC, Smith TL, Soler ZM. Establishing the minimal clinically important difference for the Questionnaire of Olfactory Disorders. Int Forum Allergy Rhinol. 2018 Sep;8(9):1041–1046.
8. Kim DW, Kim JY, Jeon SY. The Status of the olfactory cleft may predict postoperative olfactory function in chronic rhinosinusitis with nasal polyposis. Am J Rhinol Allergy. 2011 Mar;25(2):e90–94.
9. Tao X, Chen F, Sun Y, et al. Prediction models for postoperative uncontrolled chronic rhinosinusitis in daily practice. Laryngoscope. 2018 Dec;128(12):2673–80.
10. Padilla-Galo A, Olveira C, Fernández de Rota-Garcia L, et al. Factors associated with bronchiectasis in patients with uncontrolled asthma; the NOPES score: a study in 398 patients. Respir Res. 2018 Mar 16;19(1):43.
11. Li F, Wang X, Shen S, Huang K, et al. Risk factors associated with comorbid asthma in patients with chronic rhinosinusitis with nasal polyps: a cross-sectional study. BMC Pulm Med. 2022 Sep 7;22(1):338.
12. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol. 1996 Dec;49(12):1373–1379.