

## Validation of Visual Analogue Scale for loss of smell as a quick test in chronic rhinosinusitis with nasal polyps

**Short title:** VAS for loss of smell in CRSwNP

Alobid I<sup>\*1,2,3</sup>, Calvo-Henríquez C<sup>\*4,5</sup>, Viveros-Díez P<sup>6</sup>, López-Chacón M<sup>1,2,3</sup>, Rojas-Lechuga MJ<sup>2,7</sup>, Langdon C<sup>1,2,3</sup>, Marin C<sup>2,3</sup>, Mullol J<sup>2,3,7</sup>

<sup>1</sup>Skull Base Unit, ENT Department, Hospital Clinic Barcelona, IDIBAPS, CIBERES, Barcelona University, Barcelona, Catalonia, Spain

<sup>2</sup>INGENIO, IRCE, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), CIBERES, Barcelona, Catalonia, Spain

<sup>3</sup>CIBER of Respiratory Diseases (CIBERES), Institute of Health Carlos III

<sup>4</sup>Rhinology Unit, ENT Department, Hospital Complex of Santiago de Compostela, Spain

<sup>5</sup>Young-Otolaryngologists of the International Federations of Oto-rhino-laryngological Societies (YO-IFOS) study group

<sup>6</sup>ENT department, University Hospital of Valladolid, Valladolid, Spain

<sup>7</sup>Rhinology Unit & Smell Clinic, ENT Department, Hospital Clinic Barcelona, IDIBAPS, CIBERES, Barcelona, Catalonia, Spain

\*These authors share first-author responsibilities.

### Corresponding authors

Isam Alobid

Skull Base Unit

ENT Department, Hospital Clinic, Barcelona University, Spain.

[isamalobid@gmail.com](mailto:isamalobid@gmail.com)

Joaquim Mullol, MD, PhD

[jmullol@clinic.cat](mailto:jmullol@clinic.cat)

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0937

**ABSTRACT**

**INTRODUCTION/OBJECTIVE:** Diagnostic criteria of chronic rhinosinusitis with nasal polyps (CRSwNP) include, among others, olfactory dysfunction (OD). We hypothesize that patients suffering with CRSwNP are good at self-assessing their sense of smell through visual analogue scale (VAS) compared to smell tests.

**METHODS:** A controlled cross-sectional study was planned. Adults diagnosed with severe CRSwNP waiting for endoscopic sinus surgery were included. A cohort of healthy controls was also studied. All participants performed Barcelona smell test (BAST-24), sinonasal outcomes test 22 (SNOT-22), and VAS for loss of smell. CRSwNP underwent blood test (eosinophils count, total serum IgE), CT scan (Lund-Mackay Score), and nasal endoscopy.

**RESULTS:** 138 severe CRSwNP and 40 controls subjects were included. The BAST-24 identification score was strongly correlated with the VAS score in the CRSwNP group ( $\rho = -0.79$ ,  $p < 0.001$ ) but not in the control group ( $\rho = -0.14$ ;  $p = 0.39$ ), this difference between groups being statistically significant ( $p < 0.001$ ). A significant correlation of SNOT-22 item 21 (loss of smell) was also found with BAST-24 identification ( $\rho = -0.65$ ,  $p < 0.001$ ), this difference being statistically significant ( $Z = -2.43$ ;  $p = 0.015$ ). In the ROC curve, the area under the curve (AUC) was 0.85 with 72.5% sensitivity and 93.1% specificity.

**CONCLUSION.** This study demonstrates a potential role of the VAS score for the screening of OD in severe CRSwNP in daily clinical practice.

**Key words:** Polyposis. CRSwNP. Rhinosinusitis. BAST-24. Smell.

## RESUMEN

**INTRODUCCIÓN/OBJETIVO:** Los criterios diagnósticos de la rinitis crónica con pólipos nasales (CRSwNP, por sus siglas en inglés) incluyen, entre otros, la disfunción olfatoria (OD). Nuestra hipótesis es que los pacientes que padecen CRSwNP son buenos para autoevaluar su sentido del olfato a través de una escala analógica visual (VAS) en comparación con pruebas de olfato.

**MÉTODOS:** Se llevó a cabo un estudio transversal controlado. Se incluyeron adultos diagnosticados con CRSwNP grave que esperaban una cirugía endoscópica de senos nasales. También se estudió una cohorte de controles sanos. Todos los participantes realizaron la prueba de olfato de Barcelona (BAST-24), el cuestionario de resultados sinonasales 22 (SNOT-22) y la VAS para la pérdida del olfato. Los pacientes con CRSwNP se sometieron a análisis de sangre (recuento de eosinófilos, IgE sérica total), tomografía computarizada (puntuación de Lund-Mackay) y endoscopia nasal.

**RESULTADOS:** Se incluyeron 138 pacientes con CRSwNP grave y 40 sujetos de control. La puntuación de identificación de BAST-24 se correlacionó fuertemente con la puntuación de VAS en el grupo CRSwNP ( $\rho=-0,79$ ,  $p<0,001$ ), pero no en el grupo de control ( $\rho=-0,14$ ;  $p=0,39$ ), siendo esta diferencia entre grupos estadísticamente significativa ( $p<0,001$ ). También se encontró una correlación significativa del ítem 21 de SNOT-22 (pérdida del olfato) con la identificación de BAST-24 ( $\rho=-0,65$ ,  $p<0,001$ ), siendo esta diferencia estadísticamente significativa ( $Z=-2,43$ ;  $p=0,015$ ). En la curva ROC, el área bajo la curva (AUC) fue 0,85 con una sensibilidad del 72,5% y una especificidad del 93,1%.

**CONCLUSIÓN:** Este estudio demuestra un posible papel de la puntuación de VAS para la detección de OD en CRSwNP grave en la práctica clínica diaria.

**Palabras clave:** pólipos; CRSwNP; rinitis; BAST-24; olfato.

## SUMMARY BOX:

- What do we know about this topic?

Chronic rhinosinusitis patients usually have olfactory dysfunction. There is controversy if visual analogue scales can be used for the diagnosis. Up to date, no validation study has been performed exclusively in this cohort of patients.

- How does this study impact our current understanding and/or clinical management of this topic?

This study demonstrated high correlation between visual analogue scale and instrumental evaluation of the smell in the severe chronic rhinosinusitis with nasal polyps cohort ( $\rho$  0.79), but not in the healthy control cohort ( $\rho$  0.14).

Accepted Article

## INTRODUCTION

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a highly prevalent disease that affects 0.5 - 5% of the population.[1] Diagnostic criteria of chronic rhinosinusitis with (CRSwNP) and without (CRSsNP) nasal polyps include, among others, olfactory dysfunction (OD). [2,3]

On the other hand, OD is also a highly prevalent symptom. It affects approximately 5% of the general population.[4] However, this prevalence is greatly increased in patients suffering from CRSwNP,[5] where a 60-80% prevalence of loss of smell has been reported. [6]

According to EPOS guidelines, OD should be instrumentally assessed through validated smell (University of Pennsylvania Smell Identification Test / UPSIT, Sniffin' Sticks, or Barcelona smell test / BAST-24 among others). However, other guidelines such as Polina [7] also suggest visual analogue scales. These tests may be time consuming, an alternative tool to quickly assess which patients actually need a full olfactory test is necessary. There are two main options, either a short instrumental smell test or a subjective self-report.

Previous experiences have shown a poor correlation between subjective and instrumental assessment of the OD. [8] However, none of these reports were conducted exclusively in patients with CRSwNP, which is of utmost importance, as these patients have a fluctuating sense of smell. [9] It has also been reported that these patients who are more aware of their sense of smell obtain better correlations between the subjective and instrumental assessment. [8] In fact, the frequency of unawareness of OD was only 16% in CRS,[10] much lower than the 30% reported by Lötsch and Hummel(8) in a non-selected population, or 77% in elderly individuals. [11]

We hypothesize that patients suffering with CRSwNP are good at self-assessing their sense of smell through the visual analogue scale (VAS) compared to a gold standard (instrumental smell test).

## METHODS

### *Study population*

A controlled cross-sectional study was planned. Data was recorded from 2014 to 2017.

Inclusion criteria: adults (>18 years) were recruited from the rhinology unit of two tertiary referral university hospitals (Hospital Clinic, Barcelona and University Hospital of Valladolid). All

participants were diagnosed with severe CRSwNP according to the EPOS 2012 criteria, [12] and were sent to the waiting list for endoscopic sinus surgery (ESS).

There were no modifications in asthma treatment, and patients with sinonasal neoplasms, cystic fibrosis, ciliary dysfunction, or CRS without nasal polyposis were excluded from the study.

Healthy controls were selected from the skull base unit of the Hospital Clinic, Barcelona. Control group included patients (>18 years) with benign pathology of the skull base without sinonasal pathology or smell dysfunction who underwent transsphenoidal endoscopic surgery.

The study was performed in accordance with the ethical standards established in the Declaration of Helsinki and all patients signed their informed consents. The Research and Ethics Committee of the Barcelona Clinic Hospital approved the study protocol (HCB/2015/1021).

### **Outcomes**

**Demographic characteristics.** The following variables were recorded: gender, age, asthma, NSAID exacerbated respiratory disease (N-ERD), olfaction assessed through VAS and Barcelona Smell Test-24 (BAST-24), nasal polyp score, SinoNasal Outcomes Test 22 (SNOT-22), allergy, blood eosinophils count (BEC) and total IgE (IU/mL). For statistical analysis, age was categorized in 4 groups (18-30; 31-50; 51-70; and 71-90 year old).

**Barcelona Smell test (BAST-24).** BAST-24 is a smell test consisting of 24 odors located on a solid base in hermetic numbered boxes. [13]

Three different scores are obtained from this test, detection (if the individual detects an odor or not), memory (spontaneous recognition), and identification (if the patient correctly identifies the odor among 4 possible options) scores. In this study the cut-off value to consider an individual as normal or hyposmic was defined according to published normative data for different age subgroups. (13) Detection has a score of 99%, memory 54.6%, and forced choice identification 74.2% in healthy individuals. [13]

The BAST-24 was performed the week before the ESS in outpatient clinics.

### **ENT examination**

Participants were examined in the outpatient clinics of the Rhinology Unit the week before the ESS. All participants underwent nasal endoscopy. This examination was performed by a different examiner than the one who performed the smell test.

Nasal polyp size was classified using the Meltzer clinical score [14], which is a 0 to 4 polyp grading system (0 = no polyps, 1 = polyps confined to the middle meatus, 2 = multiple polyps occupying the middle meatus, 3 = polyps that extend beyond the middle meatus, 4 = polyps that completely obstruct the nasal cavity).

**Loss of smell Visual Analogue Scale (VAS).** Patients were asked to rate their OD from 0 (no impairment) to 100mm (complete loss of smell). Olfaction was rated before conducting the BAST-24.

**Sinonasal outcome test (SNOT-22).** SNOT-22 is a validated questionnaire designed to assess quality of life due to sinonasal symptoms.[15] The validated Spanish version of the questionnaire was used.[16] It was answered by patients before performing the BAST-24. The total score ranges from 0 to 110. Item 21 (loss of smell/taste) was also used to assess loss of smell (score 0-5).

**CT Scan – Lund Mackay score (LMS).** Sinonasal CT Scan was performed in both cases and controls. It was a 2 mm thick, square pixel scan.

The extent of disease was scored using the Lund Mackay score[17] by two examiners who were blinded to the results of the BAST-24. The Lund Mackay score assesses each nasal sinus separately and the ostiomeatal complex. The total score ranges from 0 to 24.

### ***Statistical Analysis***

All quantitative variables were tested for normality with the Shapiro Wilk test. The comparison between quantitative variables and dichotomic variables was performed with the t-test when a normal distribution was demonstrated or with the non-parametric variation rank sum test when they did not follow a normal distribution. The relationship between qualitative variables was studied through a chi-square test. The correlation between quantitative variables was performed through the Spearman's correlation analysis. The comparison between the different correlation coefficients was performed with the CORTESTI package for Stata.

The test performance was assessed with sensitivity, specificity, positive and negative predictive values and Youden index. A receiver operating characteristic (ROC) curve was calculated for the

VAS score. All statistical testing was two-tailed. Alpha was set to 0.05 for significance. All statistical analyses were made using STATA software v.16.1 (StataCorp, Tx, USA).

Accepted Article

## RESULTS

### *Demographic characteristics*

The study population is described in Table 1. A total of 178 participants were included (138 CRSwNP; 40 controls). The mean age was 52.3 years and 62.9% were males. CRSwNP patients were slightly older than controls. Regarding comorbid conditions in the CRSwNP group, 53.6% had concomitant asthma, 25.4% N-ERD, and 48.6% atopy (based on symptoms and skin prick test). None of the quantitative variables followed a normal distribution.

### *Olfactory data and correlations*

The BAST-24 smell identification score was strongly correlated with the VAS in the CRSwNP group ( $\rho=-0.79$ ,  $p<0.001$ ) (Figure 1) but not in the control group ( $\rho=-0.14$ ;  $p=0.39$ ), this difference between both correlations being statistically significant ( $z=5.01$ ;  $p<0.001$ ). Similar data were found in the detection score ( $\rho=-0.70$ ,  $p<0.001$ ;  $\rho=0.09$ ,  $p=0.582$ ) this difference being statistically significant ( $z=4.19$ ,  $p<0.001$ ); and memory score ( $\rho=-0.44$ ,  $p<0.001$ ;  $\rho=-0.05$ ,  $p=0.776$ ), significant difference between groups ( $z=2.28$ ,  $p<0.023$ ).

Same comparisons were assessed with the question 21 (loss of smell/taste) of the SNOT-22. There was also a significant, but lower correlation with the identification score ( $\rho=-0.65$ ,  $p<0.001$ ), detection score ( $\rho=-0.39$ ,  $p<0.001$ ) and memory score ( $\rho=-0.55$ ,  $p<0.001$ ). The differences between the correlation on the question 21, and VAS score was statistically significant ( $Z=-2.43$ ;  $p=0.015$ ).

A subgroup analysis regarding nasal polyp size in the CRSwNP group revealed a statistically significant difference ( $\chi^2=17.43$ ,  $p<0.001$ ), with worse results in BAST-24 forced-choice smell identification when increasing nasal polyp size. There was no difference in the correlation score between groups according to nasal polyp size.

A subgroup analysis according to age subgroups in CRSwNP group failed to demonstrate any statistically significant difference in BAST-24 smell identification. There was no difference in correlation score between groups.

When VAS olfactory loss is categorized according to its severity in 0-30; >30-70 and >70-100; it could only be demonstrated significant correlation in the severe cases (VAS >70-100) ( $\rho=-0.35$ ;  $p=0.002$ ). Being this difference in the correlation between groups statistically significant ( $z=2.59$ ;  $p=0.009$ ).

Subgroup analyses assessing these correlations between self-assessment of OD and BAST-24 identification score were also conducted for asthma, N-ERD, and atopy. The only significant

difference was observed for asthma ( $z=-2.09$ ,  $p=0.037$ ), with a higher correlation in non-asthmatic patients ( $\rho=-0.86$  vs  $0.73$ ).

In CRSwNP, the BAST-24 smell identification was also moderately correlated with BEC ( $\rho=-0.29$ ,  $p<0.001$ ) and the Lund Mackay score ( $\rho=0.37$ ,  $p<0.001$ ). There was no correlation with total IgE.

#### **SNOT-22 data and correlations**

In CRSwNP there was a moderate correlation between SNOT-22 and BAST-24 smell detection ( $\rho=-0.39$ ,  $p<0.001$ ), smell memory/recognition ( $\rho=-0.44$ ,  $p<0.001$ ), and smell identification ( $\rho=-0.51$ ,  $p<0.001$ ). There was no correlation ( $\rho=0.11$ ;  $0.18$ ;  $-0.05$  respectively) between those outcomes in the control group.

There was a correlation between the SNOT-22 score with the NPS, with an increase in the SNOT-22 score as the size of the polyps increases ( $\chi^2=28.01$ ,  $p<0.001$ ), but no correlation with LMS ( $p=0.208$ )

#### **Receiver operator characteristic (ROC) curve**

In CRSwNP group, the BAST-24 identification score was categorized as positive or negative following the 75% cut-off value, the normative data for patients between 50 and 60 years of age. [13] Using this cut-off value, a ROC curve was plotted (Figure 2). The area under the curve (AUC) was  $0.85\pm 0.03$ . The result with the highest number of correctly classified patients (77%) and the highest Youden index (0.66) was VAS 52 mm.

#### **Contingency table in CRSwNP**

Using a cut-off value of 75% for the BAST-24 forced-choice smell identification, and 52cm for the VAS score, a contingency table was plotted (Table 2). The positive likelihood ratio and the negative likelihood ratio were 10.51 and 0.30 respectively.

#### **IgE and BEC Subgroup analysis**

BEC was categorized using a cut-off value of 250 cells/ $\mu$ L (table 3). There was a statistically significant difference in the LMS, loss of smell VAS, BAST-24 smell identification, detection and memory scores, obtaining worse results these patients with  $>250$  eosinophils/ $\mu$ L. No differences were observed for SNOT-22 total score, SNOT-21 question 21 (despite it almost reached significance), and nasal polyp score.

When IgE was categorized using 100 UI/ml as cut-off value, a significant difference in NPS could be demonstrated, being higher in those with higher IgE values ( $z=-2.47$ ,  $p=0.014$ ); and with the SNOT-22 total score, being higher for those with higher IgE values (43.6 vs 30.7) ( $z=-2.59$ ;  $p=0.009$ ). No differences were found for LMS, loss of smell VAS, BAST-24 smell identification or detection.

### **Type 2 comorbidity subgroup analysis**

The patient cohort was categorized according to the presence/absence of asthma, N-ERD, or atopy multimorbid to the CRSwNP diagnosis (Table 4). Patients with N-ERD had a worst BAST-24 smell identification, smell detection, and smell memory/recognition ( $p<0.001$ ), and a worst loss of smell measured by VAS ( $p<0.001$ ).

## **DISCUSSION**

The main findings of this study are three. First, there is a high correlation between subjective (VAS) and instrumental (BAST-24) smell assessment in CRSwNP patients. Second, the best cutoff value for the VAS score in this study is 52 mm. Third, this correlation is influenced by other factors such as severity of OD or asthma.

The main finding of this study is the high correlation between the VAS score and the smell test in CRSwNP patients ( $\rho=-0.79$ ).

Given this result, we hypothesize that VAS score could serve as a screening test in severe CRSwNP patients. Despite OD has long ago been recognized as a prognostic factor in CRSwNP, it has recently gained notoriety, since clinical guidelines such as EUFOREA [18] and EPOS(2) include OD as a criterion for the indication of and response to the treatment with monoclonal antibodies. We suggest that olfactory VAS could serve as a method to monitor CRSwNP patients, despite results should always be confirmed by an instrumental validated olfactory test. The results presented here should be managed carefully, as data collection has been performed on a highly selected cohort (severe CRSwNP patients submitted to ESS). To date, no study comparing the correlation between VAS and smell test has been performed exclusively on CRSwNP patients. All previous studies have been performed in patients with OD or healthy volunteers. In healthy volunteers, no correlation has been demonstrated.[19]

The evidence presented here suggest that the ability of CRSwNP patients to self-rate their OD is better than of other patients suffering with OD or even healthy people (control group). Previous published studies have reported worse correlations, [20-23] ranging from 0.29 [24] to 0.64. [22] It has been recently study in COVID-19 patients, reaching a moderate 0.51 correlation [25] (while it was 0.79 in our study).

We hypothesize that patients suffering from chronic nasal inflammation are more prone to variations in their sense of smell and, consequently, more aware of it. Landis et al. have demonstrated that those patients who are more aware of their sense of smell are better at self-assessing their olfactory ability.[23] This hypothesis is reinforced by our results, since SNOT-22 item 21 was less correlated than loss of smell VAS with the BAST-24 smell identification. Despite being the exact same cohort and asking the same question (rating your loss of smell), patients performed better when they focused exclusively on assessing their sense of smell and not as part of a broader symptom assessment.

The second main finding of this study is defining a cutoff value for the VAS. In our sample, the best cut-off value for VAS was 52 mm. This result is similar to that reported by Takebayashi et al (47%) [26] but notably higher than that reported by Zou et al (6.7%) [24]. These studies had two important differences: first, the gold standard test was different (BAST-24 vs T&T and Sniffin Sticks); and second, the study population was also different (CRSwNP vs non-selected patients with olfactory disorders).

Using this cutoff value, sensitivity and specificity can be calculated. This is of utmost importance as a correlation analysis is not the best way to evaluate the performance of a screening test. As the objective of a screening test is to identify as many positives as possible, sensitivity and specificity are better measurements to evaluate its performance. Unfortunately, there is scarce information to compare our results, as only few studies have reported the sensitivity and specificity. [8,26] The largest study assessed 6,050 subjects and reported a sensitivity of 71% and a specificity of 87% for the VAS score to diagnose OD.(8) Our results were slightly better, with a similar sensitivity (72%) but an increased specificity (93%) using the BAST-24 identification score as Gold Standard.

Finally, the third main result of this study is that the observed correlation may be influenced by other factors such asthma or the severity of OD. Interestingly, in our sample, the correlation between VAS and BAST-24 was independent of age. This similar correlation according to age subgroups was surprising, as the rate of false diagnoses increases with age. [8] However, in this study, age was not related to a decrease in the correlation.

OD in CRSwNP probably occurs through two different combined mechanisms. First, mechanical obstruction of the olfactory cleft can impair airflow in the region of the olfactory cleft. [27] This hypothesis is supported by a previous meta-analysis, which demonstrates a positive effect of surgery. [28] Our study also supports this hypothesis, as we have found a significant relationship between the NPS and smell test outcomes. The second mechanism is inflammatory, as inflammation in the olfactory cleft may impair olfaction. Another meta-analysis, demonstrated a positive effect of oral and topical steroids on olfaction. [29] In our study we have also found a significant correlation between eosinophilia and the BAST-24 score. This could reflect the inflammatory process that supports this last hypothesis. [6]

### **Limitations**

This study has some limitations. First, this was a tracing study, only performed in CRSwNP patients undergoing ESS. These patients are a highly selected cohort and may not reflect the whole population of CRSwNP. A future study should be performed in a day-to-day basis, assessing the whole spectrum of patients suffering with CRSwNP.

Secondly, olfactory thresholds have not been studied since BAST-24 does not include a threshold smell test. This may not be a problem, as a meta-analysis revealed significant difference for identification test but not for threshold of sniffing sticks test in CRS patients after surgery [28], suggesting that smell identification may be better than smell threshold when analyzing olfactory dysfunction in CRS patients. However, future studies should include a threshold test in order to assess this important question.

Third, as patients are severe cases of CRSwNP, they may have been previously asked or even instrumentally assessed about their sense of smell. Given the retrospective nature of the study, this variable has not been assessed and could introduce an information bias.

Fourth, Landis et al [28] have reported a relationship between nasal airflow and the sense of smell. As patients suffering with CRSwNP have a decreased nasal airflow, it would have been interesting to perform a subgroup analysis according to the nasal airflow. Again, this is a retrospective study, and the patients included have not performed rhinomanometry.

In conclusion, this tracing study has validated the VAS score as a screening of olfactory loss in CRSwNP undergoing ESS. Future studies will increase the spectrum of patients assessed. If future large-scale studies confirm the significant association between VAS scores and smell tests in CRSwNP patients, it could be implemented in daily practice, and further confirmed by smell tests.

**Financial support**

This study was supported by grant from Fondo de Investigaciones Sanitarias de la Seguridad Social (FIS) Instituto de Salud Carlos III (PI15/00263) and CIBERES (CB06/06/0010).

**Conflict of interest**

J. Mullol is a member of national or international advisory boards and has received speaker fees or funding for clinical trials and research projects from Allakos, AstraZeneca, Genentech, GSK, Glenmark, Menarini, Mitsubishi-Tanabe, MSD, VIATRIS/MEDA Pharma, Novartis, Proctor & Gamble, Regeneron Pharmaceuticals, Inc., Sanofi-Genzyme, UCB Pharma, and Uriach/Noucor Group. I. Alobid has received honoraria for consultancy and conferences from Viartis, Roche, Sanofi, GSK, MSD, Menarini, Salvat, and Novartis. C. Calvo has received honoraria for conferences from GSK, Cinfa, and Viartis, and consultancy honoraria from Forwardontics.

## REFERENCES

1. Kim JH, Choi J, Jang SS, Wrobel BB, Ference EH. Smell and Taste Impairment in a Nationwide Sample of US Adults With Chronic Rhinosinusitis Symptoms. *OTO Open*. 2021;5(1):2473974X20986756.
2. Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. *Rhinology*. 2020 Feb 20;58(Suppl S29):1–464.
3. Mullol J, Mariño-Sánchez F, Valls M, Alobid I, Marin C. The sense of smell in chronic rhinosinusitis. *J Allergy Clin Immunol*. 2020 Mar;145(3):773–6.
4. Landis BN, Konnerth CG, Hummel T. A study on the frequency of olfactory dysfunction. *The Laryngoscope*. 2004 Oct;114(10):1764–9.
5. Kohli P, Naik AN, Harruff EE, Nguyen SA, Schlosser RJ, Soler ZM. The prevalence of olfactory dysfunction in chronic rhinosinusitis. *The Laryngoscope*. 2017 Feb;127(2):309–20.
6. Alobid I, Benítez P, Cardelús S, de Borja Callejas F, Lehrer-Coriat E, Pujols L, et al. Oral plus nasal corticosteroids improve smell, nasal congestion, and inflammation in sino-nasal polyposis. *The Laryngoscope*. 2014 Jan;124(1):50–6.
7. Alobid I, Colás C, Castillo JA, Arismendi E, Del Cuvillo A, Gómez-Outes A, et al. Spanish consensus on the management of chronic rhinosinusitis with nasal polyps (POLIposis Nasal / POLINA 2.0). *J Investig Allergol Clin Immunol*. 2023 Apr 18;0.
8. Lötsch J, Hummel T. Clinical Usefulness of Self-Rated Olfactory Performance-A Data Science-Based Assessment of 6000 Patients. *Chem Senses*. 2019 Jul 17;44(6):357–64.
9. Yu L, Jiang Y, Yan B, Fang G, Wang C, Zhang L. Predictive value of clinical characteristics in eosinophilic chronic rhinosinusitis with nasal polyps: A cross-sectional study in the Chinese population. *Int Forum Allergy Rhinol*. 2022 May;12(5):726–34.
10. Nguyen DT, Nguyen-Thi PL, Jankowski R. How does measured olfactory function correlate with self-ratings of the sense of smell in patients with nasal polyposis? *The Laryngoscope*. 2012 May;122(5):947–52.
11. Dan X, Wechter N, Gray S, Mohanty J, Croteau D, Bohr V. Olfactory dysfunction in aging and neurodegenerative diseases. *Ageing Res Rev [Internet]*. 2021 Sep [cited 2023 Jan 30];70. Available from: <https://pubmed.ncbi.nlm.nih.gov/34325072/>
12. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. *Rhinol Suppl*. 2012 Mar;(23):3 p preceding table of contents, 1–298.
13. Cardesín A, Alobid I, Benítez P, Sierra E, de Haro J, Bernal-Sprekelsen M, et al. Barcelona Smell Test - 24 (BAST-24): validation and smell characteristics in the healthy Spanish population. *Rhinology*. 2006 Mar;44(1):83–9.

14. Meltzer EO, Hamilos DL. Rhinosinusitis diagnosis and management for the clinician: a synopsis of recent consensus guidelines. *Mayo Clin Proc.* 2011 May;86(5):427–43.
15. Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. *Clin Otolaryngol Off J ENT-UK Off J Neth Soc Oto-Rhino-Laryngol Cervico-Facial Surg.* 2009 Oct;34(5):447–54.
16. de los Santos G, Reyes P, del Castillo R, Fragola C, Royuela A. Cross-cultural adaptation and validation of the sino-nasal outcome test (SNOT-22) for Spanish-speaking patients. *Eur Arch Oto-Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-Laryngol - Head Neck Surg.* 2015 Nov;272(11):3335–40.
17. Lund VJ, Mackay IS. Staging in rhinosinusitis. *Rhinology.* 1993 Dec;31(4):183–4.
18. EUFOREA consensus on biologics for CRSwNP with or without asthma - PubMed [Internet]. [cited 2021 Dec 6]. Available from: <https://pubmed.ncbi.nlm.nih.gov/31090937/>
19. Philpott CM, Wolstenholme CR, Goodenough PC, Clark A, Murty GE. Comparison of subjective perception with objective measurement of olfaction. *Otolaryngol--Head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg.* 2006 Mar;134(3):488–90.
20. Welge-Luessen A, Hummel T, Stojan T, Wolfensberger M. What is the correlation between ratings and measures of olfactory function in patients with olfactory loss? *Am J Rhinol.* 2005 Dec;19(6):567–71.
21. Seok J, Shim YJ, Rhee CS, Kim JW. Correlation between olfactory severity ratings based on olfactory function test scores and self-reported severity rating of olfactory loss. *Acta Otolaryngol (Stockh).* 2017 Jul;137(7):750–4.
22. Kim JW, Kim HS, Kim M, Kim SH, Cho SW, Kim JY. Validation of Olfactory Questionnaire in Koreans: an Alternative for Conventional Psychophysical Olfactory Tests. *J Korean Med Sci.* 2021 Feb 8;36(6):e34.
23. Landis BN, Hummel T, Hugentobler M, Giger R, Lacroix JS. Ratings of overall olfactory function. *Chem Senses.* 2003 Oct;28(8):691–4.
24. Zou LQ, Linden L, Cuevas M, Metasch ML, Welge-Lüssen A, Hähner A, et al. Self-reported mini olfactory questionnaire (Self-MOQ): A simple and useful measurement for the screening of olfactory dysfunction. *The Laryngoscope.* 2020 Dec;130(12):E786–90.
25. De Sousa Machado A, Sousa F, Silva A, Meireles L. Visual Analog Scale and Olfactory Objective Tests in Hyposmia Patients: Is There a Link? *Cureus.* 2023 Feb;15(2):e34712.
26. Takebayashi H, Tsuzuki K, Oka H, Fukazawa K, Daimon T, Sakagami M. Clinical availability of a self-administered odor questionnaire for patients with olfactory disorders. *Auris Nasus Larynx.* 2011 Feb;38(1):65–72.
27. Alt JA, Mace JC, Buniel MCF, Soler ZM, Smith TL. Predictors of olfactory dysfunction in rhinosinusitis using the brief smell identification test. *The Laryngoscope.* 2014 Jul;124(7):E259-266.

28. Zhao R, Chen K, Tang Y. Olfactory changes after endoscopic sinus surgery for chronic rhinosinusitis: A meta-analysis. *Clin Otolaryngol Off J ENT-UK Off J Neth Soc Oto-Rhino-Laryngol Cervico-Facial Surg.* 2021 Jan;46(1):41–51.
29. Banglawala SM, Oyer SL, Lohia S, Psaltis AJ, Soler ZM, Schlosser RJ. Olfactory outcomes in chronic rhinosinusitis with nasal polyposis after medical treatments: a systematic review and meta-analysis. *Int Forum Allergy Rhinol.* 2014 Dec;4(12):986–94.

Accepted Article

**FIGURES LEGENDS**

Figure 1. Dot diagram and linear regression between olfaction VAS score and BAST-24 identification score.

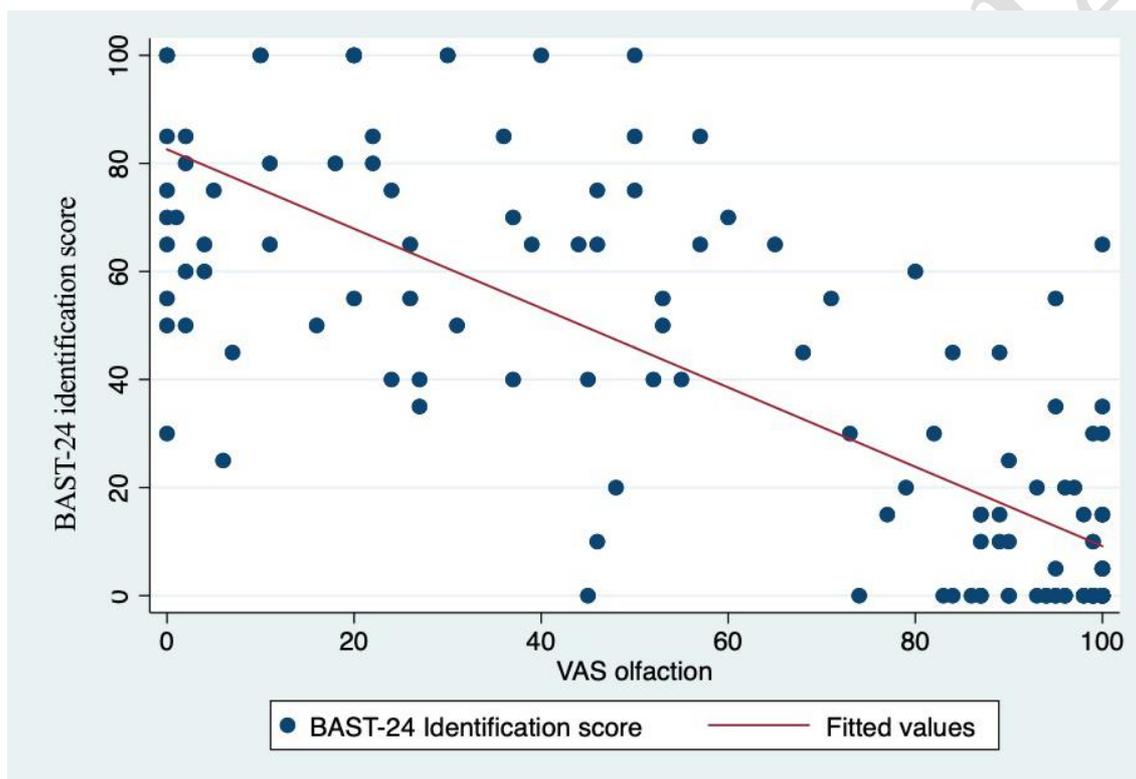
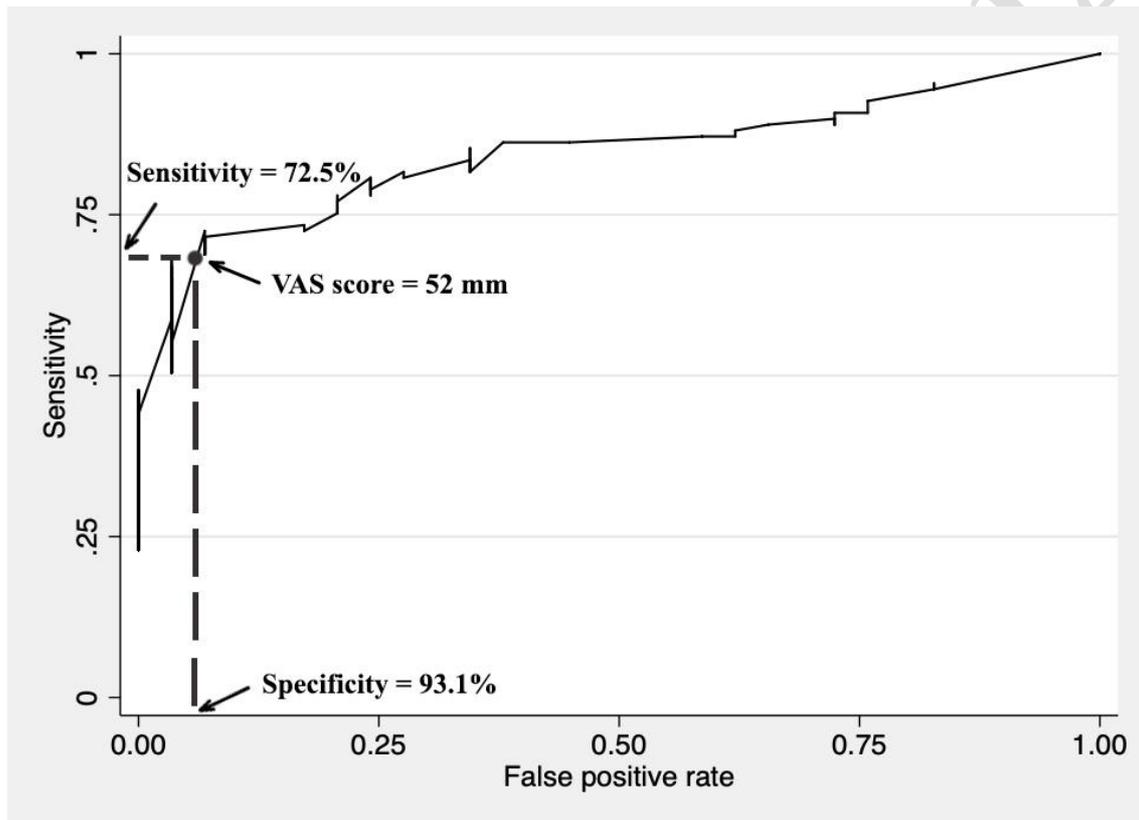


Figure 2. ROC curve for olfaction VAS score in CRSwNP patients.



**Table 1.** Characteristics of the study population

	CRSwNP (n=138)	Healthy controls (n=40)	P value
Age (years), mean (SD)	53.8 (13.1)	47.1 (13.2)	0.005
Sex (male), N (%)	86 (62.3)	26 (65.0)	0.757
Atopy, N (%)	67 (48.6)	0	<0.001
N-ERD, N (%)	35 (25.4)	0	<0.001
Asthma, N (%)	74 (53.6)	3 (7.5)	<0.001
SNOT-22 (0-110), mean (SD)	39.4 (2.1)	27.3 (3.7)	0.006
SNOT-22 item 21 (0-5), mean (SD)	3.4 (0.2)	0.7 (0.2)	<0.001
BAST-24 detection, mean (SD)	57.4 (3.6)	99.9 (0.1)	<0.001
BAST-24 identification, mean (SD)	37.9 (3.0)	64.8 (2.4)	<0.001
BAST-24 memory, mean (SD)	42.1 (3.6)	74.4 (3.5)	<0.001
Nasal polyp score, mean (SD)	4.6 (1.5)	NA	NA
Total IgE (IU/mL), mean (SD)	235.1 (387.4)	NR	NA
Lund-McKay Score (0-24), mean (SD)	15.9 (0.5)	0.5 (0.1)	<0.001
Blood EOS (%), mean (SD)	4.2 (0.4)	1.3 (0.2)	<0.001
Blood EOS (cells/ $\mu$ L), mean (SD)	574.3 (37.8)	150.3 (20.4)	<0.001

EOS, eosinophils; NSAID, non-steroidal anti-inflammatory drug; N-ERD, NSAID exacerbated respiratory disease; NA, not applicable; NR, not reported; SD, standard deviation.

**Table 2.** Contingency table in CRSwNP patients according to Visual Analogue Scale (VAS) of loss of smell and BAST-24.

	BAST-24 identification +	BAST-24 identification -	
VAS +	79	2	<b>PPV=97.5% (91.4-99.7)</b>
VAS -	30	27	<b>NPV=47.4% (34-61)</b>
	<b>Se= 72.5% (63.1-80.6)</b>	<b>Sp= 93.1% (77.2-99.2)</b>	

Se, Sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; 95% confidence interval represented between brackets.

**Table 3.** Subgroup analysis of olfactory dysfunction (BAST-24 and VAS) according to the presence of type 2 comorbidities in CRSwNP patients.

		<b>BAST-24 detection (0-100%)</b>	<b>BAST-24 Memory (0-100%)</b>	<b>BAST-24 Identification (0-100%)</b>	<b>VAS Smell loss (0-100mm)</b>
<b>CRSwNP</b>	Asthma (n=74)	53.9 ± 43.1	38.8 ± 37.3	33.3 ± 33.3	64.6 ± 37.1
	No asthma (n=63)	61.7 ± 39.8	45.9 ± 40.1	43.3 ± 36.0	56.8 ± 37.8
		z= 0.98 p= 0.328	z= 0.98 p= 0.328	z= 1.66 p= 0.096	z= -1.33 p= 0.182
<b>CRSwNP</b>	N-ERD (n=35)	32.9 ± 41.4	23.6 ± 33.1	20.7 ± 30.2	82.1 ± 28.3
	No N-ERD (n=103)	65.5 ± 38.6	47.9 ± 38.6	43.6 ± 34.5	53.9 ± 37.6
		<b>z= 3.93</b> <b>p&lt;0.001</b>	<b>z= 3.15</b> <b>p&lt;0.001</b>	<b>z= 3.4</b> <b>p&lt;0.001</b>	<b>z= -4.03</b> <b>p&lt;0.001</b>
<b>CRSwNP</b>	Atopy (n=67)	63.3 ± 40.7	49.0 ± 36.8	38.8 ± 32.0	58.2 ± 39.0
	No atopy (n=71)	52.0 ± 42.0	35.3 ± 39.5	37.1 ± 37.4	63.8 ± 36.1
		z= -1.78 p= 0.076	z= -1.78 p= 0.076	z= -0.550 p= 0.582	z= 0.60 p= 0.551

BAST-24, Barcelona Smell Test 24 odors; CRSwNP, chronic rhinosinusitis with nasal polyps; NSAID, non-steroidal anti-inflammatory drug; N-ERD, NSAID exacerbated respiratory disease; SD, standard deviation; VAS, Visual Analogue Scale; Data are presented in mean (SD).

Table 4. Subgroup analysis according to blood eosinophil count (mean (SD)) in CRSwNP patients.

	BEC <250 cells/ $\mu$ L (n=22)	BEC $\geq$ 250 cells/ $\mu$ L (n=115)	Statistical Analysis
<b>LMS (0-14)</b>	13.5 $\pm$ 5.5	16.4 $\pm$ 5.8	<b>z=-2.26, p=0.024*</b>
<b>NPS (0-8)</b>	4.5 $\pm$ 1.6	4.6 $\pm$ 1.6	z=-0.75, p=0.457
<b>Loss of smell VAS (0-100mm)</b>	45.6 $\pm$ 34.9	64.0 $\pm$ 37.4	<b>z=-2.22, p=0.027*</b>
<b>BAST-24 detection (0-100%)</b>	80.0 $\pm$ 30.1	53.4 $\pm$ 42.0	<b>z=2.47, p=0.014*</b>
<b>BAST-24 memory (0-100%)</b>	63.1 $\pm$ 32.24	38.8 $\pm$ 38.6	<b>z=2.19, p=0.028*</b>
<b>BAST-24 identification (0-100%)</b>	56.7 $\pm$ 32.5	34.5 $\pm$ 34.2	<b>z=2.78, p=0.005*</b>
<b>SNOT-22 score (0-110)</b>	39.2 $\pm$ 26.4	39.4 $\pm$ 24.4	z=-0.16, p=0.870
<b>SNOT-22 item 21 (0-5)</b>	2.6 $\pm$ 1.9	3.5 $\pm$ 1.7	z=-1.88, p=0.059

BAST-24, Barcelona Smell Test 24 odors; CRSwNP, chronic rhinosinusitis with nasal polyps; LMS, Lund-McKay Score; NPS, Nasal Polyp Size; SD, standard deviation; VAS, Visual Analogue Scale; Data are presented in mean (SD).