The Laryngoscope

Phantosmia May Predict Long-Term Measurable Olfactory Dysfunction After COVID-19

Jai-Sen Leung, MD; Valentina Paz Cordano, MD; Eduardo Fuentes-López, PhD; Antonia Elisa Lagos, MD; Francisco Gustavo García-Huidobro, MD; Rodrigo Aliaga, MD; Luis Antonio Díaz, MD; Tamara García-Salum, PhD; Erick Salinas, NP; Adriana Toro, NP; Claudio Andrés Callejas, MD; Arnoldo Riquelme, MD; James N. Palmer, MD; Rafael A. Medina, PhD; Claudia González G, MD

Objectives: Persistent olfactory dysfunction (OD) after 6 months caused by SARS-CoV-2 infection has been reported with a variable prevalence worldwide. This study aimed to determine the prevalence of long-term OD and identify predisposing factors.

Methods: A prospective cohort study was conducted on 100 adults with COVID-19. Olfactory function was assessed with the University of Pennsylvania Smell Identification Test and a symptom survey at the onset of disease and 30 days later. Patients with persistent quantitative OD at the second assessment were reevaluated after 1 year. Demographic variables, symptoms, and the degree of smell loss were analyzed.

Results: Participants included 100 patients. The mean age was 42.2 ± 15.6 years, 55 (55%) were female, and 56 (56%) were outpatients. Baseline smell loss was identified in 75/100 (75%) patients, decreasing to 39/95 (40%) after 1 month, and persisting in 29 patients after 1 year. Phantosmia at baseline was the only risk factor identified for persistent OD after 1 year (relative risk 2.51; 95% confidence interval 1.53–4.12; $p < 0.001$). Regardless of the outcome in smell function, a significant decline in olfaction was associated with the presence of phantosmia at 1 month ($\beta = -12.39$; 95% CI −19.82 to −4.95; $p < 0.01$).

Conclusions: SARS-CoV-2 (2019–2020 variants) produced a highly frequent OD that persisted in 29% of the patients after 1 year. The presence of phantosmia at baseline and 1 month was associated with a worse evolution, but phantosmia may interfere with the performance in an identification smell test. A longer follow-up is required in these patients.

Key Words: anosmia, COVID-19, hyposmia, olfaction disorders.

Level of Evidence: 2

***Laryngoscope*, 00:1–8, 2022**

INTRODUCTION

Olfactory dysfunction (OD) is one of the most common symptoms of COVID-19, with a reported prevalence ranging from 0% to 98%[1,2] for the initial viral variants during 2019 and 2020. Studies that assessed OD using psychophysical tests have found higher prevalence rates than subjective reports,[3] which can be attributed to patient bias in studies evaluating the self-reported smell perception.[4–7]

OD secondary to COVID-19 in most cases regresses spontaneously during the first 2 weeks.[3,8] However, recent evidence shows that up to 20% of the patients have persistent OD at 6 months after disease onset,[7] which may impact the long-term quality of life of millions of individuals worldwide. It is still unclear if this long-term prevalence could be considered definitive, since other post-viral olfactory disorders recover over 1–3 years after the infection.[7,9]

From the Otolaryngology Department, School of Medicine (J.-S.L., V.P.C., A.E.L., F.G.G.-H., R.A., C.A.C., C.G.G.), Pontificia Universidad Católica de Chile, Santiago, Chile; Carrera de Fonoaudiología, Departamento de Ciencias de la Salud, Faculty of Medicine (E.F.-LóPEZ., A.R.), Pontificia Universidad Católica de Chile, Santiago, Chile; Departamento de Gastroenterología, School of Medicine (L.A.D., A.R.), Pontificia Universidad Católica de Chile, Santiago, Chile; Department of Pediatric Infectious Diseases and Immunology, School of Medicine (T.G.-S., E.S., R.A.M.), Pontificia Universidad Católica de Chile, Santiago, Chile; Advanced Interdisciplinary Rehabilitation Register (AIRR) - COVID-19 Working Group, Faculty of Medicine (T.G.-S., E.S., A.R., R.A.M., C.G.G.), Pontificia Universidad Católica de Chile, Santiago, Chile; Pediatric Service, Clínica UC San Carlos, Red Salud UC-Christus, Faculty of Medicine (A.T.), Pontificia Universidad Católica de Chile, Santiago, Chile; Rhinology Division, Department of Otorhinolaryngology-Head and Neck Surgery, Perelman School of Medicine (J.N.P.), University of Pennsylvania, Philadelphia, Pennsylvania, U.S.A.; and the Department of Microbiology (R.A.M.), Icahn School of Medicine at Mount Sinai, New York, New York, U.S.A.

Additional supporting information may be found in the online version of this article.

Editor's Note: This Manuscript was accepted for publication on August 22, 2022.

C.G.G. and R.A.M. contributed equally to this work.

This work was supported by the Otorhinolaryngology Department, P. Universidad Católica de Chile, FLUOMICS Consortium, NIH-NIAID grant U19A1135972, and the Center for Research on Influenza Pathogenesis, an NIH-funded CEIRS contract HHSN272201400008C, ANID FONDECYT 1212023 to RAM, and Division of Rhinology and Endoscopic Skull Base Surgery, Department Otolaryngology-Head Neck Surgery, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, U.S.A.

The authors have no other funding, financial relationships, or conflicts of interest to disclose.

Send correspondence to Claudia González G, MD, Pontificia Universidad Católica de Chile, Diagonal Paraguay 362, 7mo piso Otorrinolaringología, Santiago Centro, Santiago 8330033, Chile. E-mail: clau_gonzalez@me.com; Rafael A. Medina, PhD, Pontificia Universidad Católica de Chile, Centro de Investigaciones Médicas, Marcoleta 391, Santiago 8330024, Chile. E-mail: rmedinai@uc.cl

DOI: 10.1002/lary.30391

Severe smell loss due to COVID-19 has been associated with mild disease, decreased need for hospitalization, and lower mortality rates.[10] In contrast, persistent OD at 6 months is associated with the initial severity of smell loss, the number of days with a positive PCR, and being of female sex.[11,12]

On the other hand, qualitative smell disorders, such as parosmia and phantosmia may occur in combination with quantitative OD. Parosmia may have a prognostic value in olfaction recovery, while there is no evidence that phantosmia is related to a specific diagnosis or prognostic value.[13] For COVID-19, previous reports have described the presence of parosmia and phantosmia in both acute and late disease.[14–19]

To date, there are only a few studies with long-term follow-up of COVID-19 patients using self-reported symptoms and psychophysical tests. Therefore, this study aimed to determine the prevalence of post-COVID-19 persistent OD in a cohort of 100 individuals. We also sought to identify potential associations between patient symptoms, demographic variables, ambulatory versus hospitalized treatment, the degree of initial smell loss, and the presence of qualitative smell disturbance with short-term (30 days) and long-term (1 year) OD persistence.

MATERIALS AND METHODS

Participants

A prospective cohort study was conducted in patients over 18 years old, with a positive COVID-19 diagnosis confirmed by a quantitative real-time polymerase chain reaction test from a nasopharyngeal swab, performed within 15 days since the onset of symptoms. Ambulatory and hospitalized patients were included. Exclusion criteria were patients with significant respiratory distress impeding them to answer, cognitive impairment or other conditions that interfere with undertaking the smell test, history of a traumatic brain injury, sinonasal and/or brain cancer, multiple sclerosis, chronic rhinosinusitis, nasal polyps, current chemotherapy, autoimmune disease with sinonasal involvement, previous olfactory loss, schizophrenia, and Parkinson's or Alzheimer's disease. The initial follow-up of this cohort at 1 month since the onset of symptoms was previously published.[20]

Patients were enrolled between April and August 2020 at the *Red de Salud UC-CHRISTUS* (Santiago, Chile), regardless of the self-perception of their olfactory function at the moment of the interview. Ambulatory patients were selected from the institutional report of positive COVID-19 cases.

This study was reviewed and approved by the Scientific Ethics Committee for Health Sciences at Pontificia Universidad Católica de Chile (ID: 200414009) before patient enrollment. Informed written consent was obtained from all the participants.

Procedures

One hundred patients at the time of enrollment (T_1) were obtained, demographic data, COVID-19 symptoms, and medical history. A survey was also conducted to evaluate chemosensory self-perception symptoms. On the same date, the olfactory function was assessed using the Spanish-American version of the 40-odorant University of Pennsylvania Smell Identification Test (UPSIT) (Sensonics International, Haddon Hts., NJ) ($_{T1}$UPSIT). The initial survey and UPSIT were applied during the hospitalization for inpatients, while ambulatory patients (at enrollment or follow-up) were evaluated in their houses. These procedures were repeated 30 days after symptom onset (T_2). Patients were no longer followed up if the $_{T2}$UPSIT was normal. Patients with an abnormal $_{T2}$UPSIT score were reassessed 1 year after the COVID-10 onset (T_3) with a new UPSIT($_{T3}$UPSIT) and survey (Fig. 1). All the data were de-identified.

Chemosensory self-perception symptoms. At T_1, T_2, and T_3, a 10-question survey was applied, including questions regarding the present olfactory function status, nasal obstruction, olfactory function evolution since the previous survey, gustatory dysfunction, xerostomia, and the presence of phantosmia and parosmia.[20] Since there are no validated patient-reported outcome measures in Spanish to assess distorted odor perception, we formulated questions regarding the presence, characteristics, and evolution of qualitative olfactory symptoms (Table S1).

Psychophysical smell test. The Spanish-American version of the 40-odorant UPSIT was applied for olfactory testing. The UPSIT is a well-validated and reliable test (test–retest $r = 0.94$).[21,22] The test is a booklet with embedded odors in the paper that are released by scratching the paper surface. Patients must identify the smell using the "forced option" modality within a list of items. A 10% (4 points) or greater change in the UPSIT score was considered clinically significant.[23] The UPSIT was previously applied to a control group of Chilean patients, establishing a cut-off score of 33 points (25th percentile).[11,20,24]

Statistical Analysis

Demographic and clinical characteristics were expressed as mean and standard deviation for continuous variables, and frequency distribution for categorical variables. Fisher's exact test was used to compare the proportions of nasal symptoms and chemosensory dysfunction at baseline and follow-up. Dunn's test was used to conduct multiple comparisons between different time assessments for the continuous variables. All analyses were adjusted by multiple comparisons using Bonferroni's Multiple Comparison Test. Trends in the proportion of nasal symptoms and chemosensory dysfunction were evaluated using the Cochran-Armitage nonparametric test for trend.

Univariate, multivariable linear, and binomial regression models were built to assess the association between primary outcomes and each of the independent variables of interest. The mean difference, relative risk (RR), and 95% confidence interval (CI) were determined. The standard error of linear regression models was estimated through bootstrapping (10,000 replications).

Since symptoms in consecutive measures for the same subject were compared, an intra-subject correlation was expected, producing biased estimates in the linear multivariable model. Therefore, when estimating the variance–covariance matrix, it was specified that the observations were clustered, allowing for intragroup correlation and relaxing the usual requirement that the observations be independent.

Statistical analyses were performed using the Stata software version 17.0 (StataCorp, 2021) and RStudio version 1.1.4 (RStudio Team, 2018).

RESULTS

To assess the prevalence of persistent OD after COVID-19, 100 patients were enrolled, of which 56% (56) were ambulatory and 44% (44) were inpatients. Five patients were lost at the 1-month follow-up (one was transferred to the intensive care unit and four withdrew from the study), hence the final sample size was 95 patients. Of these, 39 patients had OD after 30 days

since disease onset, of which three withdrew at the 1-year follow-up, and 36 completed the study (Fig. 1). Demographic characteristics of the cohort are shown in Table I.

Measurements were performed at 9 ± 3.2 (range 2–15) days (T_1), at 30.8 ± 2.2 (range 27–40) days (T_2), and at 356 ± 43 (range 271–449) days (T_3) after the onset of COVID-19 symptoms.

Self-Reported Symptoms

At T_1, smell loss was self-reported in 73% (73/100) of patients. At T_2, 24.2% (23/95) reported persistent OD. Among patients with an abnormal $_{T2}$UPSIT, 66% (24/36) reported normal olfaction at T_3 in the symptom survey, while 22.2% (8/36) considered they had a worse smell function since the previous assessment.

Other upper airway and chemosensory symptoms and their frequency are summarized in Table II. While most of the symptoms improved after a month or a year, the proportion of patients with parosmia remained unchanged (T_1: 17% [17/100]; T_2: 15% [14/95]; and T_3: 19% [7/36]; $p = 0.80$), and phantosmia significantly increased after 1 year (T_1: 11% [11/100]; T_2: 5% [5/95]; and T_3: 31% [11/36]; $p < 0.01$).

Psychophysical Evaluation

The $_{T1}$UPSIT was abnormal in 75% (75/100) of the COVID-19 patients, decreasing to 41% (39/95) at T_2. The mean $_{T1}$UPSIT score was 28.07 ± 7.0, improving to 32.8 ± 3.4 at T_2 ($p < 0.001$). Of those patients with initial OD, 46.6% (35/75) normalized at T_2, at which time there was a clinically relevant improvement in the UPSIT score

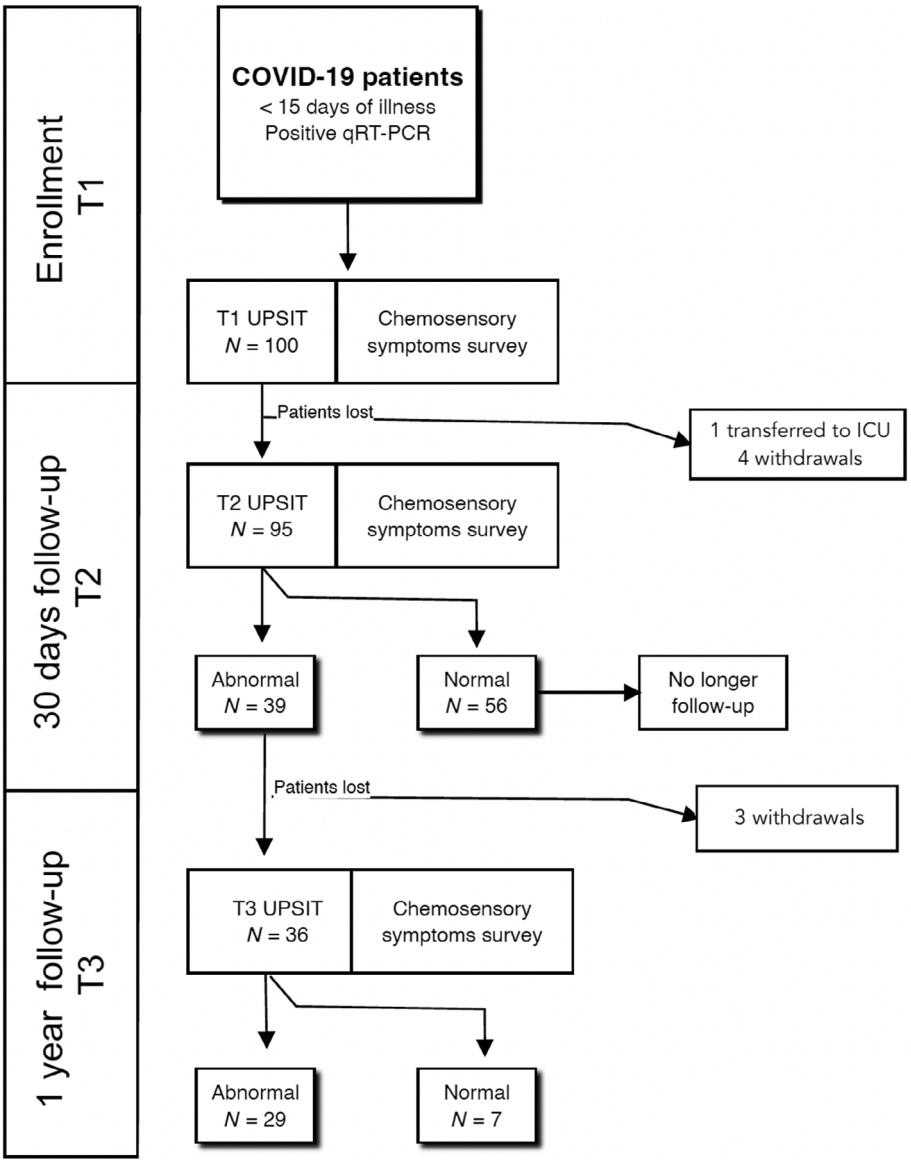

Fig. 1. Flow chart showing the cohort design, follow-up strategy and number of patients at each time point. ICU = intensive care unit; qRT-PCR = quantitative real-time polymerase chain reaction; UPSIT = University of Pennsylvania Smell Identification Test.

TABLE I.
Demographic and Baseline Characteristics of Patients Infected With SARS-CoV-2 at Enrollment.

Characteristics	Patients ($n = 100$)
Gender, *N* (%)	
Female	55 (55)
Male	45 (45)
Age, mean (SD)	42.2 (±15.6)
Female, mean (SD)	43.2 (±16.7)
Male, mean (SD)	40.9 (±13.8)
Comorbidities or conditions, *N* (%)	
Smoker	12 (12)
Allergic diseases	18 (18)
Diabetes	10 (10)
Cardiovascular diseases/hypertension	18 (18)
Chronic pulmonary diseases (Asthma, COPD)	11 (11)
Rheumatologic diseases	7 (7)
ACE inhibitors	10 (10)
Immunosuppressive therapy	4 (4)
General COVID-19 symptoms, *N* (%)	
Cough	75 (75)
Myalgia	74 (74)
Fever	61 (61)
Dyspnea	43 (43)
Headache	81 (81)
Nausea/vomiting	35 (35)
Severe fatigue	58 (58)
Diarrhea	36 (36)
Chills	52 (52)
Anorexia	22 (22)
Rhinorrhea	37 (37)
Odynophagia	39 (39)
Postnasal drip	18 (18)

ACE = angiotensin-converting enzyme; COPD = Chronic obstructive pulmonary disease; SD = standard deviation.

in 40% (38/95) of patients, while in 5% (5/95) of individuals it declined.

In the subgroup of patients tested at T_3 ($n = 36$), 80.5% (29/36) had an abnormal $_{T3}$UPSIT. The mean UPSIT score significantly improved in this subgroup between T_1: 26.42 ± 6.9 and T_3: 29.61 ± 4.3 ($p < 0.05$). However, the average UPSIT score did not significantly improve from T_2 to T_3 ($p = 0.630$) (Fig. 2). Between T_2 and T_3, there was a clinically relevant improvement in UPSIT score in 8.3% (3/36) of patients, while in 11.1% (4/36) of individuals, it declined.

When assessing OD severity at T_1, T_2, and T_3 (Fig. 3), the proportion of patients with mild microsomia was higher at T_3: 44.4% (16/36) versus T_2: 22.1% (21/95), $p < 0.05$. Conversely, there was no significant difference when comparing T_1 versus T_3 ($p = 0.187$). In addition, no significant change was noted for moderate microsomia at T_2: 15.7% (15/95) and T_3: 25% (9/36; $p = 0.93$); severe microsomia at T_2: 3.1% (3/95) and T_3: 8.3% (3/36; $p = 1.00$); or anosmia at T_2: 0% (0/95) and T_3: 2.7% (1/36; $p = 0.824$).

Variables Associated With Persistent OD

The univariate linear model showed a decreased relative risk for persistent OD at T_3 in patients with mild disease (not requiring hospitalization) (RR 0.53; 95% CI 0.29–0.99; $p < 0.05$) and an increased relative risk in patients with phantosmia at T_1 (RR 2.57; 95% CI 1.45–4.58; $p < 0.01$). No significant association was observed for age, gender, comorbidities, COVID-19 symptoms, initial UPSIT score, and nasal obstruction (Table III). The multivariable model showed that the only relative risk factor for persistent OD was the presence of phantosmia at T_1 (RR 2.51; 95% CI 1.53–4.12; $p < 0.001$).

Variables Associated With Improvement in Olfactory Function

Olfactory function improvement, regardless of its final status, was assessed at follow-up. The univariate linear model showed a significant olfactory improvement in ambulatory COVID-19 patients ($\beta = 4.49$; 95% CI 1.92–7.40; $p < 0.001$), and patients with dysgeusia during COVID-19 ($\beta = 3.99$; 95% CI 1.31–7.13; $p < 0.01$). On the other hand, a decline in olfactory function was significantly associated with age ($\beta = -0.11$; 95% CI −0.20 to −0.03; $p < 0.05$), the presence of phantosmia at T_2 ($\beta = -7.58$; 95% CI −15.99 to −1.75; $p < 0.05$), and phantosmia at 1-year follow-up ($\beta = -5.64$; 95% CI −10.91 to −0.96; $p < 0.05$) (Table IV). In the case of the $_{T1}$UPSIT score, a better initial result was associated with a smaller improvement in olfaction at 1 year ($\beta = -0.82$; 95% CI −0.96 to −0.69; $p < 0.001$). The multivariable linear regression analysis showed that the $_{T1}$UPSIT score and phantosmia at T_2 were associated with a significant improvement in olfactory function. Nevertheless, only phantosmia at T_2 showed a clinically relevant difference (score difference > 4 points).

DISCUSSION

Our study demonstrates a prevalent smell dysfunction in 29% of the studied cohort who are still suffering from impaired olfaction 1 year after COVID-19. Moreover, the presence of phantosmia was associated with a greater risk of persistent OD after 1 year since the onset of symptoms and a decline in quantitative smell function measured by an identification smell test.

Among patients with smell impairment caused by COVID-19, a temporal improvement in olfactory function has been reported worldwide. Measured normosmia has been shown to improve from 4% at onset to 61% at 1 month,[8] 23% to 72% at 6 months,[7,25,26] and 54% at 1 year of follow-up after infection.[27] In our cohort, normosmia was observed in 59% of patients at 30 days and in 78.5% at 1 year of follow-up. However, we did not follow patients who normalized their olfaction after 1 month; hence, we cannot rule out a decline in the smell function in that group over time. When analyzing self-reported symptoms, subjective OD has been reported to decrease by 41% at 6 months[28] and 25.8% at 1 year of follow-up.[29] Nevertheless, self-reported OD may be

TABLE II.
Self-Reported Nasal and Chemosensory Symptoms of SARS-CoV-2 Infected Patients at Baseline and Follow-Up.

Variables	Baseline (T_1) ($n = 100$) *N* (%)	1-Mo Follow-Up (T_2) ($n = 95$) *N* (%)	*p*-Value T_1 Versus T_2*	1-Year Follow-Up (T_3) ($n = 36$) *N* (%)	*p*-Value T_1 Versus T_3*	*p*-Value T_2 Versus T_3*	*p*-for the Trend†
Nasal obstruction	61 (61)	37 (39)	<0.01	12 (33)	<0.05	1.00	<0.01
Chemosensory symptoms							
Parosmia	17 (17)	14 (15)	1.00	7 (19)	1.00	1.00	0.80
Phantosmia	11 (11)	5 (5)	0.580	11 (31)	<0.05	<0.001	<0.01
Dry mouth	62 (62)	16 (17)	<0.001	7 (19)	<0.001	1.00	<0.001
Burning mouth	11 (11)	4 (4)	0.32	2 (6)	1.00	1.00	0.20
Bitter taste	32 (32)	8 (8)	<0.001	6 (17)	0.262	0.622	<0.05
Salty taste	3 (3)	2 (2)	1.00	0 (0)	1.00	1.00	0.29
Acid taste	7 (7)	1 (1)	0.20	0 (0)	0.57	1.00	<0.05
Pharyngeal globus	29 (29)	13 (14)	<0.05	7 (19)	1.00	1.00	0.13
Taste impairment self-perception	51 (51)	24 (25)	<0.001	5 (14)	<0.001	0.714	<0.001
Sweet	36 (36)	13 (14)	<0.01	3 (8)	<0.01	1.00	<0.001
Salty	36 (36)	10 (11)	<0.001	2 (6)	<0.01	1.00	<0.001
Acid	25 (25)	9 (9)	<0.05	1 (3)	<0.01	0.850	<0.001
Bitter	27 (27)	10 (11)	<0.05	1 (3)	<0.01	0.864	<0.001

*Values obtained through the Fisher exact test adjusted by multiple comparisons (Bonferroni method).
†Values obtained through the Dunn's test adjusted by multiple comparisons (Bonferroni method).

unreliable and subject to patient bias.[4] In our cohort, 66% of the patients assessed after 1 year reported normal olfactory function, however, the UPSIT score was abnormal at 80.5%, emphasizing the need for a psychophysical test to assess abnormal olfactory function. To date, the reported recovery rate of OD after COVID-19 seems higher than other post-infectious smell disorders, where the cumulative olfactory cure rate has been shown to be 23.6% at 6 months, 33.7% at 12 months, and 61% at 30 months.[30] Nonetheless, a longer follow-up is required to determine the actual prevalence of persistent OD in COVID-19,[31] as further improvement has been described in other post-infectious OD during the second year of disease onset[32] or after.[33,34] The present study is ongoing and will continue to follow-up these individuals to assess the natural history of persistent OD due to COVID-19.

The exact pathophysiology of olfactory injury caused by SARS-CoV-2 infection is complex and still unknown,[35] with diverse theories proposed for it.[36,37] Our analyses showed that COVID-19 outpatients had a decreased risk of persistent OD 1 year after the onset of symptoms. A significant improvement in olfactory function was more likely in patients with a lower baseline olfactory function. The same observation was recently described in a study that assessed 246 patients.[38] In our previous study,[20] outpatients had more profound smell loss and were younger

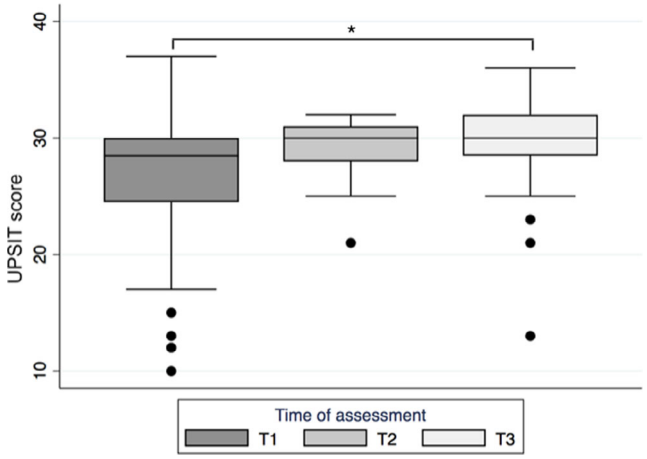

Fig. 2. Olfactory function (University of Pennsylvania Smell Identification Test [UPSIT] score) evolution post-COVID-19 in the subgroup of patients who were evaluated up to 1 year after disease onset ($n = 36$). Box plot graph showing the median (line in the box) and 25 and 75 percentiles (whiskers). Black dots are showing outliers. T_1: Baseline (range 2–15 days); T_2: 1-month follow-up (range 27–40 days) and T_3: 1-year follow-up (range 271–449 days).

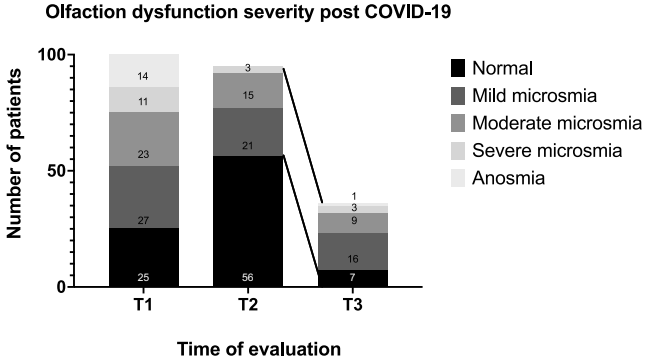

Fig. 3. Olfactory dysfunction severity post-COVID-19. Each column represents a different time point, showing the number of patients with normal University of Pennsylvania Smell Identification Test (UPSIT) scores; mild, moderate, severe microsomia, or anosmia.

TABLE III.
Univariate and Multivariable Binomial Regression Analysis for Variables That may Increase the Risk of Persistent Olfactory Dysfunction (Abnormal $_F$UPSIT Score).

	Univariate		Multivariable*	
Variable	Relative Risk (95% CI)	*p*-Value	Relative Risk (95% CI)	*p*-Value
Age	1.02 (1.00–1.04)	0.090	1.01 (0.96–1.02)	0.177
Gender				
Male	Reference	—		
Female	0.76 (0.41–1.41)	0.388		
COVID-19 severity				
Hospitalized	**Reference**	**—**	Reference	—
Ambulatory	**0.53 (0.29–0.99)**	**<0.05**	0.67 (0.35–1.28)	0.226
Smoking	0.88 (0.31–2.48)	0.802		
Rhinitis	0.71 (0.28–1.83)	0.479		
Asthma	0.67 (0.19–2.40)	0.534		
Dysgeusia	0.78 (0.42–1.45)	0.432		
Parosmia				
Baseline (T_1)	1.27 (0.61–2.65)	0.517		
1 Mo follow-up (T_2)	1.21 (0.55–2.63)	0.638		
1 Year follow-up (T_3)	0.86 (0.52–1.42)	0.562		
Phantosmia				
Baseline (T_1)	**2.57 (1.45–4.58)**	**<0.01**	**2.51 (1.53–4.12)**	**<0.001**
1 Mo follow-up (T_2)	1.33 (0.44–4.08)	0.614		
1 Year follow-up (T_3)	1.02 (0.73–1.44)	0.897		
Nasal obstruction				
Baseline (T_1)	0.68 (0.37–1.26)	0.222		
1 Mo follow-up (T_2)	0.83 (0.43–1.57)	0.559		
1 Year follow-up (T_3)	0.90 (0.62–1.31)	0.579		
Initial UPSIT score	0.98 (0.94–1.01)	0.213		

Variables significantly associated with the outcome are shown in bold.
*Multivariable regression model constructed with all the significant variables. Age was also included considering a borderline *p*-value.
CI = confidence intervals; UPSIT = University of Pennsylvania Smell Identification Test.

than hospitalized patients. The same association between anosmia and mild disease has been previously established,[39] leading to the hypothesis that a more significant OD can be caused by a robust immune response in the upper respiratory tract and olfactory epithelium, which might protect individuals from severe disease.[40] High levels of proinflammatory cytokines like TNF-α[41] and interleukin-6[42] have been identified in anosmic patients with COVID-19, supporting this theory, where inflammation may cause a more profound OD that improves slowly over time. Outpatients also showed a significant and clinically relevant improvement in olfactory function (more than 4 points difference in the UPSIT score), regardless of normalization. More extensive population studies and longer follow-up periods are warranted to confirm these observations and to clarify the role of age, the degree of smell loss in COVID-19 severity, and olfaction recovery rate.

Qualitative symptoms of smell impairment, such as parosmia and phantosmia, are commonly associated with post-viral OD.[43] They seem to occur during states of neuronal degeneration or regeneration.[44,45] Currently, parosmia is a common complaint at the otolaryngology clinic in patients who had COVID-19, with a reported prevalence varying from 11% to 43%.[14–17] In our cohort, the proportion of patients suffering from parosmia did not improve during the follow-up period. However, we did not follow patients that normalized their olfaction after 1 month since the onset of symptoms. Thus, our results might underestimate the prevalence of this symptom after 1 year in these individuals. Parosmia has been associated with a better prognosis for olfaction recovery in other post-viral ODs.[43,46,47] In our study, at the short-term follow-up (4–6 weeks), parosmia was more common in the group of patients with unresolved smell loss and was found to be a predictor of non-remission.[15] Our analysis did not reveal an association of parosmia with persistent OD at 1 year or a significant improvement in smell function.

Interestingly, the proportion of patients with phantosmia increased after 1 year and it was still present in 31% of our final cohort, considering the follow-up limitations stated before. Furthermore, baseline phantosmia increased the risk of persistent OD at 1 year, and its presence at 1 month was associated with a clinically relevant decline in olfactory function. Phantosmia has been recently described in COVID-19 patients,[18] with a variable reported prevalence, ranging from 11.8% at 6 months of follow-up[16] to 20.5% between 100 and 244 days following

TABLE IV.
Univariate and Multivariable Linear Regression Analysis for Variables Associated With Olfactory Function Improvement ($_{F}$UPSIT–$_{T1}$UPSIT).*

Variable	Univariate			Multivariable†,‡		
	Mean Difference (95% CI)	*p*-Value	R^2	Mean Difference (95% CI)	*p*-Value	R^2
Age	**−0.11 (−0.20 to −0.03)**	**<0.05**	**4.90**	−0.02 (−0.10 to 0.05)	0.547	83.63
Gender						
Male	Reference	—	2.59			
Female	2.31 (−0.75 to 4.88)	0.110				
COVID-19 severity						
Hospitalized	**Reference**	**—**	**9.60**	Reference	—	
Ambulatory	**4.49 (1.92–7.40)**	**<0.001**		−0.10 (−2.44 to 2.33)	0.926	
Smoking	1.94 (−2.91 to 8.50)	0.493	0.87			
Dysgeusia	**3.99 (1.31–7.13)**	**<0.01**	**7.72**	2.10 (−0.17 to 4.37)	0.071	
Qualitative chemosensory symptoms						
Parosmia at baseline (T_1)	−0.98 (−4.81 to 3.45)	0.644	0.26			
Parosmia at 1 mo follow-up (T_2)	−0.14 (−4.46 to 6.80)	0.959	0.01			
Parosmia at 1 year follow-up (T_3)	8.98 (−2.44 to 16.73)	0.066	18.80			
Phantosmia at baseline (T_1)	−3.51 (−8.17 to 2.24)	0.178	2.46			
Phantosmia at 1 mo follow-up (T_2)	**−7.58 (−15.99 to −1.75)**	**<0.05**	**5.57**	**−12.39 (−19.82 to −4.95)**	**<0.01**	
Phantosmia at 1 year follow-up (T_3)	**−5.64 (−10.91 to −0.96)**	**<0.05**	**11.31**	−1.96 (−5.11 to 1.19)	0.224	
Nasal obstruction						
At baseline (T_1)	0.30 (−2.90 to 3.21)	0.852	0.04	0.34 (−2.16 to 3.43)	0.810	
At 1 mo follow-up (T_2)	**−2.83 (−5.19 to −0.12)**	**<0.05**	**3.72**			
At 1 year follow-up (T_3)	0.33 (−5.02 to 7.25)	0.914	0.04			
Initial UPSIT score	**−0.82 (−0.96 to −0.69)**	**<0.001**	**66.71**	**−0.86 (−1.04 to −0.62)**	**<0.001**	

Variables significantly associated with the outcome are shown in bold.
*The standard error of linear regression models was estimated through bootstrapping (10,000 replications). The 95% CI were calculated using the bias-corrected and accelerated method.
†Multivariable regression model constructed with all the significant variables. Age was also included considering a borderline *p*-value. The explained variance of the multivariate linear regression model (adjusted R^2) reached 83.63%.
‡The variance–covariance matrix was estimated, specifying that the observations were clustered, allowing for intragroup correlation.
CI = confidence intervals; UPSIT = University of Pennsylvania Smell Identification Test.

COVID-19.[19] This symptom has also been associated with histopathological changes in the olfactory epithelium.[48,49] These results should be carefully interpreted, given that the presence of persistent qualitative smell symptoms may represent an ongoing regeneration process. This observation suggests the need for longer follow-up studies, as more time is required to attribute a prognostic role for parosmia or phantosmia in the outcome of the final smell function. Olfactory epithelium biopsies in patients with phantosmia have shown that they have decreased nerve fascicle density and fibrosis, which could explain its association with persistent OD.[50] Thus, these findings raise another critical consideration; such patients should undergo additional assessment using tools like a threshold smell test, given that parosmia and phantosmia can overestimate the smell loss by decreasing the patient's performance when an identification test is applied.[38]

The present study has the following limitations: (1) Follow-up was stopped when the smell was recovered after 1 month since the onset of symptoms, and continued only in those patients who persisted with measurable OD. Hence, we cannot rule out further changes in the olfactory function or smell qualitative symptoms in individuals with an early and complete recovery. (2) We did not include a threshold and discrimination test that would have helped to better understand this disease. However, due to safety concerns at the beginning of the COVID-19 pandemic, we decided not to introduce tests where the stimulus is placed at a short distance from the nose of individuals and is then reused between patients.

CONCLUSION

COVID-19 produced persistent OD in 29% of our cohort at a 1-year follow-up evaluation. The presence of phantosmia was associated with persistent OD 1 year after the disease, however, this symptom may alter the identification of odorants, interfering with the test results. It is necessary to extend the follow-up time period to determine if the OD is definitive whereas other post-infectious smell dysfunctions regress more than 1 year after the infection. Our data suggests that patients with OD secondary to COVID-19 should be referred to specialists for rehabilitation and follow-up.

BIBLIOGRAPHY

1. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. 2020;77(6):683-690. https://doi.org/10.1001/jamaneurol.2020.1127.

2. Lechien JR, Chiesa-Estomba CM, de Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol*. 2020;277(8):2251-2261. https://doi.org/10.1007/s00405-020-05965-1.
3. Boscutti A, Delvecchio G, Pigoni A, et al. Olfactory and gustatory dysfunctions in SARS-CoV-2 infection: a systematic review. *Brain Behav Immun Health*. 2021;15:100268. https://doi.org/10.1016/j.bbih.2021.100268.
4. Landis BN, Hummel T, Hugentobler M, Giger R, Lacroix JS. Ratings of overall olfactory function. *Chem Senses*. 2003;28(8):691-694. https://doi.org/10.1093/chemse/bjg061.
5. Hummel T, Whitcroft KL, Andrews P, et al. Position paper on olfactory dysfunction. *Rhinology*. 2017;54:1-30. https://doi.org/10.4193/Rhino16.248.
6. Vaira LA, Deiana G, Fois AG, et al. Objective evaluation of anosmia and ageusia in COVID-19 patients: single-center experience on 72 cases. *Head Neck*. 2020;42:1252-1258. https://doi.org/10.1002/hed.26204.
7. Boscolo-Rizzo P, Menegaldo A, Fabbris C, et al. Six-month psychophysical evaluation of olfactory dysfunction in patients with COVID-19. *Chem Senses*. 2021;46:bjab006. https://doi.org/10.1093/chemse/bjab006.
8. Moein ST, Hashemian SMR, Tabarsi P, Doty RL. Prevalence and reversibility of smell dysfunction measured psychophysically in a cohort of COVID-19 patients. *Int Forum Allergy Rhinol*. 2020;10(10):1127-1135. https://doi.org/10.1002/alr.22680.
9. Lee DY, Lee WH, Wee JH, Kim JW. Prognosis of postviral olfactory loss: follow-up study for longer than one year. *Am J Rhinol Allergy*. 2014;28(5):419-422. https://doi.org/10.2500/ajra.2014.28.4102.
10. Goyal R, Kapoor A, Goyal MK, Singh R. Alteration of smell and taste sensations in Covid-19 positive patients: a prospective cohort study in western India. *Indian J Otolaryngol Head Neck Surg*. 2021;73(3):371-377. https://doi.org/10.1007/s12070-021-02670-1.
11. Ugurlu BN, Akdogan O, Yilmaz YA, et al. Quantitative evaluation and progress of olfactory dysfunction in COVID-19. *Eur Arch Otorhinolaryngol*. 2021;278(7):2363-2369. https://doi.org/10.1007/s00405-020-06516-4.
12. Boscolo-Rizzo P, Guida F, Polesel J, et al. Self-reported smell and taste recovery in coronavirus disease 2019 patients: a one-year prospective study. *Eur Arch Otorhinolaryngol*. 2022;279:515-520. https://doi.org/10.1007/s00405-021-06839-w.
13. Landis BN, Frasnelli J, Croy I, Hummel T. Evaluating the clinical usefulness of structured questions in parosmia assessment. *Laryngoscope*. 2010;120(8):1707-1713. https://doi.org/10.1002/lary.20955.
14. Raad N, Ghorbani J, Safavi Naeini A, Tajik N, Karimi-Galougahi M. Parosmia in patients with COVID-19 and olfactory dysfunction. *Int Forum Allergy Rhinol*. 2021;11(10):1497-1500. https://doi.org/10.1002/alr.22818.
15. Makaronidis J, Firman C, Magee CG, et al. Distorted chemosensory perception and female sex associate with persistent smell and/or taste loss in people with SARS-CoV-2 antibodies: a community based cohort study investigating clinical course and resolution of acute smell and/or taste loss in people with and without SARS-CoV-2 antibodies in London, UK. *BMC Infect Dis*. 2021;21(1):221. https://doi.org/10.1186/s12879-021-05927-w.
16. Ercoli T, Masala C, Pinna I, et al. Qualitative smell/taste disorders as sequelae of acute COVID-19. *Neurol Sci*. 2021;42(12):4921-4926. https://doi.org/10.1007/s10072-021-05611-6.
17. Hopkins C, Surda P, Vaira LA, et al. Six month follow-up of self-reported loss of smell during the COVID-19 pandemic. *Rhinology*. 2021;59(1):26-31. https://doi.org/10.4193/Rhin20.544.
18. İşlek A, Balcı MK. Phantosmia with COVID-19 related olfactory dysfunction: report of nine case. *Indian J Otolaryngol Head Neck Surg*. 2021;1-3. https://doi.org/10.1007/s12070-021-02505-z.
19. Schambeck SE, Crowell CS, Wagner KI, et al. Phantosmia, parosmia, and dysgeusia are prolonged and late-onset symptoms of COVID-19. *J Clin Med*. 2021;10(22):5266. https://doi.org/10.3390/jcm10225266.
20. González C, García-Huidobro FG, Lagos AE, et al. Prospective assessment of smell and taste impairment in a south-American coronavirus disease 2019 (COVID-19) cohort: association with the need for hospitalization and reversibility of dysfunction. *Int Forum Allergy Rhinol*. 2021;11(8):1273-1277. https://doi.org/10.1002/alr.22798.
21. Doty RL, Shaman P, Dann M. Development of the University of Pennsylvania Smell Identification Test: a standardized microencapsulated test of olfactory function. *Physiol Behav*. 1984;32(3):489-502. https://doi.org/10.1016/0031-9384(84)90269-5.
22. Doty RL, Frye RE, Agrawal U. Internal consistency reliability of the fractionated and whole University of Pennsylvania Smell Identification Test. *Percept Psychophys*. 1989;45(5):381-384. https://doi.org/10.3758/bf03210709.
23. Doty RL, Reyesq PF, Gregor T. Presence of both odor identification and detection deficits in Alzheimer's disease. *Brain Res Bull*. 1987;18(5):597-600. https://doi.org/10.1016/0361-9230(87)90129-8.
24. Fornazieri MA, dos Santos CA, Bezerra TFP, de Rezende Pinna F, Voegels RL, Doty RL. Development of normative data for the Brazilian adaptation of the University of Pennsylvania smell identification test. *Chem Senses*. 2015;40(2):141-149. https://doi.org/10.1093/chemse/bju068.
25. Petrocelli M, Cutrupi S, Salzano G, et al. Six-month smell and taste recovery rates in coronavirus disease 2019 patients: a prospective psychophysical study. *J Laryngol Otol*. 2021;135(5):436-441. https://doi.org/10.1017/S002221512100116X.
26. Prem B, Liu DT, Besser G, et al. Long-lasting olfactory dysfunction in COVID-19 patients. *Eur Arch Otorhinolaryngol*. 2022;279(7):3485-3492. https://doi.org/10.1007/s00405-021-07153-1.
27. Boscolo-Rizzo P, Hummel T, Hopkins C, et al. High prevalence of long-term olfactory, gustatory, and chemesthesis dysfunction in post-COVID-19 patients: a matched case-control study with one-year follow-up using a comprehensive psychophysical evaluation. *Rhinology*. 2021;59(6):517-527. https://doi.org/10.4193/Rhin21.249.
28. Bertlich M, Stihl C, Lüsebrink E, et al. The course of subjective and objective chemosensory dysfunction in hospitalized patients with COVID-19: a 6-month follow-up. *Eur ArchOtorhinolaryngol*. 2021;278:4855-4861. https://doi.org/10.1007/s00405-021-06796-4.
29. Fortunato F, Martinelli D, Iannelli G, et al. Self-reported olfactory and gustatory dysfunctions in COVID-19 patients: a 1-year follow-up study in Foggia district, Italy. *BMC Infect Dis*. 2022;22(1):77. https://doi.org/10.1186/s12879-022-07052-8.
30. Ogawa T, Nakamura K, Yamamoto S, Tojima I, Shimizu T. Recovery over time and prognostic factors in treated patients with post-infectious olfactory dysfunction: a retrospective study. *Ann Otol Rhinol Laryngol*. 2020;129(10):977-982. https://doi.org/10.1177/0003489420922563.
31. Dicpinigaitis PV. Post-viral anosmia (loss of sensation of smell) did not begin with COVID-19! *Lung*. 2021;199(3):237-238. https://doi.org/10.1007/s00408-021-00448-4.
32. Rombaux P, Huart C, Deggouj N, Duprez T, Hummel T. Prognostic value of olfactory bulb volume measurement for recovery in postinfectious and posttraumatic olfactory loss. *Otolaryngol Head Neck Surg*. 2012;147(6):1136-1141. https://doi.org/10.1177/0194599812459704.
33. Duncan HJ, Seiden AM. Long-term follow-up of olfactory loss secondary to head trauma and upper respiratory tract infection. *Arch Otolaryngol Head Neck Surg*. 1995;121(10):1183-1187. https://doi.org/10.1001/archotol.1995.01890100087015.
34. London B, Nabet B, Fisher AR, White B, Sammel MD, Doty RL. Predictors of prognosis in patients with olfactory disturbance. *Ann Neurol*. 2008;63(2):159-166. https://doi.org/10.1002/ana.21293.
35. Lee JC, Nallani R, Cass L, Bhalla V, Chiu AG, Villwock JA. A systematic review of the neuropathologic findings of post-viral olfactory dysfunction: implications and novel insight for the COVID-19 pandemic. *Am J Rhinol Allergy*. 2021;35(3):323-333. https://doi.org/10.1177/1945892420957853.
36. Xydakis MS, Albers MW, Holbrook EH, et al. Post-viral effects of COVID-19 in the olfactory system and their implications. *Lancet Neurol*. 2021;20(9):753-761. https://doi.org/10.1016/S1474-4422(21)00182-4.
37. DosSantos MF, Devalle S, Aran V, et al. Neuromechanisms of SARS-CoV-2: a review. *Front Neuroanat*. 2020;14:37. https://doi.org/10.3389/fnana.2020.00037.
38. Liu DT, Sabha M, Damm M, et al. Parosmia is associated with relevant olfactory recovery after olfactory training. *Laryngoscope*. 2021;131(3):618-623. https://doi.org/10.1002/lary.29277.
39. Purja S, Shin H, Lee JY, Kim E. Is loss of smell an early predictor of COVID-19 severity: a systematic review and meta-analysis. *Arch Pharm Res*. 2021;44(7):725-740. https://doi.org/10.1007/s12272-021-01344-4.
40. Sanli DET, Altundag A, Kandemirli SG, et al. Relationship between disease severity and serum IL-6 levels in COVID-19 anosmia. *Am J Otolaryngol*. 2021;42(1):102796. https://doi.org/10.1016/j.amjoto.2020.102796.
41. Torabi A, Mohammadbagheri E, Akbari Dilmaghani N, et al. Proinflammatory cytokines in the olfactory mucosa result in COVID-19 induced anosmia. *ACS Chem Neurosci*. 2020;11(13):1909-1913. https://doi.org/10.1021/acschemneuro.0c00249.
42. Cazzolla AP, Lovero R, Lo Muzio L, et al. Taste and smell disorders in COVID-19 patients: role of interleukin-6. *ACS Chem Neurosci*. 2020;11(17):2774-2781. https://doi.org/10.1021/acschemneuro.0c00447.
43. Reden J, Maroldt H, Fritz A, Zahnert T, Hummel T. A study on the prognostic significance of qualitative olfactory dysfunction. *Eur Arch Otorhinolaryngol*. 2006;264(2):139-144. https://doi.org/10.1007/s00405-006-0157-0.
44. Croy I, Nordin S, Hummel T. Olfactory disorders and quality of life–an updated review. *Chem Senses*. 2014;39(3):185-194. https://doi.org/10.1093/chemse/bjt072.
45. Cho SH. Clinical diagnosis and treatment of olfactory dysfunction. *Hanyang Med Rev*. 2014;34(3):107. https://doi.org/10.7599/hmr.2014.34.3.107.
46. Cavazzana A, Larsson M, Münch M, Hähner A, Hummel T. Postinfectious olfactory loss: a retrospective study on 791 patients. *Laryngoscope*. 2018;128(1):10-15. https://doi.org/10.1002/lary.26606.
47. Hummel T, Lotsch J. Prognostic factors of olfactory dysfunction. *Arch Otolaryngol Head Neck Surg*. 2010;136(4):347-351. https://doi.org/10.1001/archoto.2010.27.
48. Leopold DA, Schwob JE, Youngentob SL, Hornung DE, Wright HN, Mozell MM. Successful treatment of phantosmia with preservation of olfaction. *Arch Otolaryngol Head Neck Surg*. 1991;117(12):1402-1406. https://doi.org/10.1001/archotol.1991.01870240094016.
49. Leopold DA, Loehrl TA, Schwob JE. Long-term follow-up of surgically treated phantosmia. *Arch Otolaryngol Head Neck Surg*. 2002;128(6):642-647. https://doi.org/10.1001/archotol.128.6.642.
50. Holbrook EH, Leopold DA, Schwob JE. Abnormalities of axon growth in human olfactory mucosa. *Laryngoscope*. 2005;115(12):2144-2154. https://doi.org/10.1097/01.MLG.0000181493.83661.CE.