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 (β = -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

INTRODUCTION

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

OD secondary to COVID-19 in most cases regresses spontaneously during the first 2 weeks. However, recent evidence shows that up to 20% of the patients have persistent OD at 6 months after disease onset, 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.

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 Fonacuiludio, 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., E.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., E.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 (U.P.), University of Pennsylvania, Philadelphia, Pennsylvania, U.S.A.; and the Department of Microbiology (E.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.

This was supported by the Otorhinolaryngology Department, P. Universidad Católica de Chile, FLUOMICS Consortium, NIH-NIAID grant U19AI135972, and the Center for Research on Influenza PATHogenesis, an NIH-funded CRiRS contract HHSN272201400008C; ANID PONDECYT 1210293 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, Mar celibina 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{13} For COVID-19, previous reports have described the presence of parosmia and phantosmia in both acute and late disease.\textsuperscript{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.

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 or follow-up were evaluated in their houses. These procedures were repeated 30 days after symptom onset (T2). 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 (T3) with a new UPSIT (T2 UPSIT) and survey (Fig. 1). All the data were de-identified.

Chemosensory self-perception symptoms. At T1, T2, and T3, 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.\textsuperscript{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–testest $r = 0.94$).\textsuperscript{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.\textsuperscript{23} The UPSIT was previously applied to a control group of Chilean patients, establishing a cut-off score of 33 points (25th percentile).\textsuperscript{11,20,24}

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.\textsuperscript{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 (T1) 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) (Sensomics International, Haddon Hts., NJ) ($\tau_{1}$ 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 (T2). Patients were no longer followed up if the $\tau_{2}$ UPSIT was normal. Patients with an abnormal $\tau_{2}$ UPSIT score were reassessed 1 year after the COVID-10 onset (T3) with a new UPSIT ($\tau_{2}$ UPSIT) and survey (Fig. 1). All the data were de-identified.
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 (T1), at 30.8 ± 2.2 (range 27–40) days (T2), and at 356 ± 43 (range 271–449) days (T3) after the onset of COVID-19 symptoms.

**Self-Reported Symptoms**

At T1, smell loss was self-reported in 73% (73/100) of patients. At T2, 24.2% (23/95) reported persistent OD. Among patients with an abnormal T2UPSIT, 66% (24/36) reported normal olfaction at T3 in the symptom survey, while 22.2% (8/36) considered they had a worse smell function since the previous assessment.

**Psychophysical Evaluation**

The T1UPSIT was abnormal in 75% (75/100) of the COVID-19 patients, decreasing to 41% (39/95) at T2. The mean T1UPSIT score was 28.07 ± 7.0, improving to 32.8 ± 3.4 at T2 (p < 0.001). Of those patients with initial OD, 46.6% (35/75) normalized at T2, at which time there was a clinically relevant improvement in the UPSIT score.

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 (T1: 17% [17/100]; T2: 15% [14/95]; and T3: 19% [7/36]; p = 0.80), and phantosmia significantly increased after 1 year (T1: 11% [11/100]; T2: 5% [5/95]; and T3: 31% [11/36]; p < 0.01).
in 40% (38/95) of patients, while in 5% (5/95) of individuals it declined.

In the subgroup of patients tested at T3 (n = 36), 80.5% (29/36) had an abnormal T3UPSIT. The mean UPSIT score significantly improved in this subgroup between T1: 26.42 ± 6.9 and T3: 29.61 ± 4.3 (p < 0.05). However, the average UPSIT score did not significantly improve from T2 to T3 (p = 0.630) (Fig. 2). Between T2 and T3, 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 T1, T2, and T3 (Fig. 3), the proportion of patients with mild microsomia was higher at T3: 44.4% (16/36) versus T2: 22.1% (21/95), p < 0.05. Conversely, there was no significant difference when comparing T1 versus T3 (p = 0.187). In addition, no significant change was noted for moderate microsomia at T3: 15.7% (15/95) and T2: 25% (9/36; p = 0.93); severe microsomia at T3: 3.1% (3/95) and T2: 8.3% (3/36; p = 1.00); or anosmia at T2: 0% (0/95) and T3: 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 T3 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 T1 (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 T1 (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 (β = 4.49; 95% CI 1.92–7.40; p < 0.001), and patients with dysgeusia during COVID-19 (β = 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 (β = −0.11; 95% CI −0.20 to −0.03; p < 0.05), the presence of phantosmia at T2 (β = −7.58; 95% CI −15.99 to −1.75; p < 0.05), and phantosmia at 1-year follow-up (β = −5.64; 95% CI −10.91 to −0.96; p < 0.05) (Table IV). In the case of the T1UPSIT score, a better initial result was associated with a smaller improvement in olfaction at 1 year (β = −0.82; 95% CI −0.96 to −0.69; p < 0.001). The multivariable linear regression analysis showed that the T1UPSIT score and phantosmia at T2 were associated with a significant improvement in olfactory function. Nevertheless, only phantosmia at T2 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 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 months28 and 25.8% at 1 year of follow-up.29 Nevertheless, self-reported OD may be
unreliable and subject to patient bias. 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. Nonetheless, a longer follow-up is required to determine the actual prevalence of persistent OD in COVID-19 as further improvement has been described in other post-infectious OD during the second year of disease onset or after. 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, with diverse theories proposed for it. 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. In our previous study, outpatients had more profound smell loss and were younger.

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

| Variables                        | Baseline (T1) (n = 100) N (%) | 1-Mo Follow-Up (T2) (n = 95) N (%) | p-Value T1 Versus T2 | 1-Year Follow-Up (T3) (n = 36) N (%) | p-Value T1 Versus T3 | p-Value T2 Versus T3 | p-Value T1 Versus T2 Versus T3 | 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 |                               |                                   |                     |                                     |                     |                     |                               |                |
| Sweet                            | 51 (51)                       | 24 (25)                           | <0.001              | 5 (14)                              | <0.001              | 0.714               | <0.001                        |                |
| Salty                            | 36 (36)                       | 13 (14)                           | <0.01               | 3 (8)                               | <0.01               | 1.00                | <0.001                        |                |
| Acid                             | 36 (36)                       | 10 (11)                           | <0.001              | 2 (6)                               | <0.01               | 1.00                | <0.001                        |                |
| Bitter                           | 25 (25)                       | 9 (9)                             | <0.05               | 1 (3)                               | <0.01               | 0.850               | <0.001                        |                |
| Taste impairment self-perception |                               |                                   |                     |                                     |                     |                     |                               |                |
| 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               | 0.864               | <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).
than hospitalized patients. The same association between anosmia and mild disease has been previously established, 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.

High levels of proinflammatory cytokines like TNF-α and interleukin-6 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. They seem to occur during states of neuronal degeneration or regeneration. 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%. 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.

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. Our analysis did not reveal an association of parosmia with persistent OD at 1 year or as 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, with a variable reported prevalence, ranging from 11.8% at 6 months of follow-up to 20.5% between 100 and 244 days following

| Variable                  | Univariate Relative Risk (95% CI) | p-Value | Multivariable 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                        |         |                                    |         |
| 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 (T₁)             | 1.27 (0.61–2.65)                 | 0.517   |                                    |         |
| 1 Mo follow-up (T₂)       | 1.21 (0.55–2.63)                 | 0.638   |                                    |         |
| 1 Year follow-up (T₃)     | 0.86 (0.52–1.42)                 | 0.562   |                                    |         |
| Phantosmia                |                                  |         |                                    |         |
| Baseline (T₁)             | 2.57 (1.45–4.58)                 | <0.01   | 2.51 (1.53–4.12)                   | <0.001  |
| 1 Mo follow-up (T₂)       | 1.33 (0.44–4.08)                 | 0.614   |                                    |         |
| 1 Year follow-up (T₃)     | 1.02 (0.73–1.44)                 | 0.897   |                                    |         |
| Nasal obstruction         |                                  |         |                                    |         |
| Baseline (T₁)             | 0.68 (0.37–1.26)                 | 0.222   |                                    |         |
| 1 Mo follow-up (T₂)       | 0.83 (0.43–1.57)                 | 0.559   |                                    |         |
| 1 Year follow-up (T₃)     | 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.
COVID-19. This symptom has also been associated with histopathological changes in the olfactory epithelium. 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. 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.

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.
25. Petrocelli M, Cutrupi S, Salzano G, et al. Six-month smell and taste recovery in COVID-19 patients: a prospective cohort study. Eur Arch Otorhinolaryngol. 2021;278(7):2251-2261. https://doi.org/10.1007/s00405-021-05865-1.

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/s00405-022-05391-7.

27. Boscolo-Rizzo P, Hummel T, Hopkins C, et al. High prevalence of long-term olfactory dysfunction, gustatory dysfunction, and chemesthesia dysfunction in post-COVID-19 patients: a matched cohort study of one-year follow-up using a comprehensive psychophysical evaluation. Rhinology. 2021;59(6):517-527. https://doi.org/10.14193/Rhinol21.249.

28. Bertlich M, Stahl C, Lisebrink E, et al. The course of subjective and objective chemosensory dysfunction in hospitalized patients with COVID-19: a 6-month follow-up. Eur Arch Otorhinolaryngol. 2021;278:4855-4861. https://doi.org/10.1007/s00405-021-06796-4.

29. Foroni 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):177. https://doi.org/10.1186/s12879-022-07052-8.

30. Ogawa T, Nakamura K, Yamamoto S, Tujima I, Shimizu T. Recovery over time and prognostic factors in treated patients with post-infecitious olfactory dysfunction: a retrospective study. Ann Otol Rhinol Laryngol. 2020;129(8):677-682. https://doi.org/10.1177/0003489419892596.

31. Diepniagatis PV. Post-viral anosmia (loss of sensation of smell) did not begin with COVID-19. Lang. 2021;199(3):237-238. https://doi.org/10.1007/s10071-020-02448-4.

32. Rembuxa P, Haart C, Degqun J, Hummel T. Prognostic value of olfactory bulb volume measurement for recovery in postinfectious and posttraumatic olfactory dysfunction. Otolaryng Head Neck Surg. 2012;147(6):136-141. https://doi.org/10.1177/0194599612450794.

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.1995.0180010007015.

34. Kim JC, Nallani R, Cass L, Bhalla V, Chiu AG, Villwock JA. A systematic review of the neuropathologic findings of post-olfactory dysfunction: implications for novel insight for the COVID-19 pandemic. Am J Rhinol Allergy. 2021;35(3):323-333. https://doi.org/10.1177/194594920957853.

35. Yaxakis 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.

36. DoSantos MF, Devalle S, Aran V, et al. Neuromechanisms of SARS-CoV-2: a review. Front Neurol. 2020;11(47). https://doi.org/10.3389/fnana.2019.00007.

37. Liu DT, Sahra M, Damm M, et al. Parosmia is associated with relevant olfactory recovery at 6 months post-COVID. Lancet Respir Med. 2021;3(3):418-423. https://doi.org/10.1016/S2213-2600(20)30277-7.

38. 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.

39. Sanii DET, Almeghrab A, Almekhlaifi S, et al. Relationship between disease severity and serum IL-6 levels in COVID-19 anosmia. Am J Otolaryngol. 2021;42(10):1273-1277. https://doi.org/10.1016/j.amjol.2021.102796.

40. Torabi A, Mohammadbigheri E, Akbari Dilmaghani N, et al. Proinflammatory cytokines in the olfactory mucosa result in COVID-19 induced anosmia. ACS Chem Neurosci. 2020;11(13):2009-2013. https://doi.org/10.1021/acs.chemneuro.0c00299.

41. Cazzella AP, Lovero L, Bo Muzio L, et al. Taste and smell disorders in COVID-19 patients: role of interferon-alpha. Chem Senses. 2021;46(13):1277-1281. https://doi.org/10.1093/chemse/bbj006.

42. Reden J, Maroldt H, Fritz A, Zahner T, Hummel T. A study on the prognostic significance of qualitative olfactory dysfunction. Eur Arch Otorhinolaryngol. 2020;277(10):139-144. https://doi.org/10.1007/s00405-020-05266-0.

43. 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/bju072.