


Prevalence of Persistent Olfactory Disorders in Patients With COVID-19: A Psychophysical Case-Control Study With 1-Year Follow-up

Luigi Angelo Vaira, MD^{1,2} , Giovanni Salzano, MD^{1,3}, Serge Daniel Le Bon, MD⁴, Angelantonio Maglio, MD⁵, Marzia Petrocelli, MD⁶, Younes Steffens, MD⁴, Enrica Ligas, MSN¹, Fabio Maglitta, MD^{1,3}, Jerome R. Lechien, MD, PhD^{7,8}, Sven Saussez, MD, PhD⁸, Alessandro Vatrella, MD⁵, Francesco Antonio Salzano, MD⁹, Paolo Boscolo-Rizzo, MD¹⁰, Claire Hopkins, FRSC (ORLHNS), DM (Oxon)¹¹, and Giacomo De Riu, MD, FEBOMFS^{1,2}

Abstract

The purpose of this multicenter case-control study was to evaluate a group of patients at least 1 year after coronavirus disease 2019 (COVID-19) with Sniffin' Sticks tests and to compare the results with a control population to quantify the potential bias introduced by the underlying prevalence of olfactory dysfunction (OD) in the general population. The study included 170 cases and 170 controls. In the COVID-19 group, 26.5% of cases had OD (anosmia in 4.7%, hyposmia in 21.8%) versus 3.5% in the control group (6 cases of hyposmia). The TDI score (threshold, discrimination, and identification) in the COVID-19 group was significantly lower than in the control group (32.5 [interquartile range, 29-36.5] vs 36.75 [34-39.5], $P < .001$). The prevalence of OD was significantly higher in the COVID-19 group, confirming that this result is not due to the underlying prevalence of OD in the general population.

Keywords

COVID-19, olfactory, smell, anosmia, SARS-CoV-2, long COVID-19, coronavirus, prospective study, PS/QI.

Received September 3, 2021; accepted November 3, 2021.

Emerging prospective studies have reported a significant rate of coronavirus disease 2019 (COVID-19)-related persistent olfactory dysfunction (POD) 6 months after onset,¹⁻⁸ ranging from 1% to 59%. However, as these studies do not include preinfection assessment or control populations, it has not been possible to quantify the potential bias introduced by the underlying prevalence of olfactory dysfunction (OD) in the general population, which is around 20%.⁹ Moreover, only a few studies are based on psychophysical tests,^{2,5,8} and it has been shown that self-report olfactory loss alone is not a reliable index of olfactory function.¹⁰

Furthermore, recovery is still expected to continue up to and beyond 12 months after onset, necessitating longer-term studies.¹¹ The purpose of this study was to evaluate a group of patients with psychophysical tests at least 1 year after SARS-CoV-2 infection and to compare the results with a control population.

Materials and Methods

This multicenter study (ethical approval PG/2021/7118; University of Cagliari) was conducted in 4 hospitals: Sassari,

¹Maxillofacial Surgery Operative Unit, Department of Medical, Surgical and Experimental Sciences, University of Sassari, Sassari, Italy

²Biomedical Science PhD School, Biomedical Science Department, University of Sassari, Sassari, Italy

³Maxillofacial Surgery Unit, University Hospital of Naples Federico II, Naples, Italy

⁴Department of Otorhinolaryngology and Head and Neck Surgery, CHU de Bruxelles, CHU Saint-Pierre, School of Medicine, Université Libre de Bruxelles, Brussels, Belgium

⁵Respiratory Diseases Operative Unit, Department of Medicine, Surgery and Dentistry, Scuola Medica Salernitana, University of Salerno, Baronissi, Italy

⁶Maxillofacial Surgery Operative Unit, Bellaria and Maggiore Hospital-AUSL of Bologna, Bologna, Italy

⁷Department of Otolaryngology-Head Neck Surgery, Foch Hospital, Paris Saclay University, Paris, France

⁸Department of Human and Experimental Oncology, Faculty of Medicine UMONS Research Institute for Health Sciences and Technology, University of Mons, Mons, Belgium

⁹Otolaryngology Operative Unit, Department of Medicine, Surgery and Dentistry, Scuola Medica Salernitana, University of Salerno, Baronissi, Italy

¹⁰Department of Medical, Surgical and Health Sciences, Section of Otolaryngology, University of Trieste, Trieste, Italy

¹¹King's College, London, UK

Corresponding Author:

Luigi Angelo Vaira, Maxillofacial Surgery Operative Unit, Department of Medical, Surgical and Experimental Sciences, University of Sassari, Viale San Pietro 43/B, Sassari, 07100, Italy.

Email: lavaira@uniss.it

Table 1. Clinical Assessment Results and Statistical Analysis.^a

	COVID-19	Control	P value ^b
Age, y, mean ± SD	39.9 ± 10.5	38.8 ± 14.1	.471 ^c
Sex			>.99
Male	70 (41.2)	70 (41.2)	
Female	100 (58.8)	100 (58.8)	
Self-reported olfactory loss during infection	119 (70)		
Psychophysical test results			
Normal	125 (73.5)	164 (96.5)	
Hyposmia	37 (21.8)	6 (3.5)	<.001
Anosmia	8 (4.7)	0 (0)	
TDI score, ^d median (IQR)	32.5 (29-36.5)	36.75 (34-39.5)	<.001
Self-reported			
Olfactory loss	44 (25.9)	0 (0)	<.001
Parosmia	42 (24.7)	2 (11.7)	<.001
Phantosmia	39 (22.9)	0 (0)	<.001
Gustatory dysfunction	33 (19.4)	1 (0.6)	<.001

Abbreviations: IQR, interquartile range; TDI, threshold, discrimination, and identification.

^aValues are presented as No. (%) unless noted otherwise.

^bP values are based on Fisher's exact test unless noted otherwise.

^cMann-Whitney *U* test.

^dTDI scoring system: TDI score ≤ 16.5 anosmia, TDI score > 30.5 normosmia, TDI score between these two values hyposmia.

Salerno, and Bologna (Italy) and Brussels (Belgium). The study population was composed of subjects with a polymerase chain reaction–confirmed diagnosis of SARS-CoV-2 infection at least 1 year before enrollment. To avoid selection bias, consecutive subjects were enrolled from the lists provided by the prevention departments. The controls consisted of health care workers who did not have a previous diagnosis or suspicion of SARS-CoV-2 infection. Controls were matched to cases by age (±2 years) and sex.

For both groups, the exclusion criteria were previous OD and history of neurologic or nasal and paranasal sinus pathologies. All subjects included in the study underwent psychophysical evaluation of smell using the extended version of the Sniffin' Sticks test as previously described.^{9,12} The prevalence of parosmia, phantosmia, and gustatory dysfunctions was assessed by asking patients to self-report their presence or absence.

The sample size was calculated on a predicted prevalence of OD in 29% of cases^{1,2,5,6,8} and 16% of controls,⁹ with 80% power and a 5% margin of error, resulting in a minimum sample size of 161 subjects for each study group. The Mann-Whitney *U* test was performed to evaluate the differences in olfactory scores between the study groups and univariate regression analysis to assess the correlations between age/sex and TDI scores (threshold, discrimination, and identification; statistical significance at *P* ≤ .05 with a 95% CI).

Results

The study included 170 cases and 170 controls (**Table 1**). The mean ± SD time from COVID-19 diagnosis was 419.8 ± 49.4 days. At psychophysical testing, 26.5% of the subjects in the COVID-19 group had OD (anosmia in 4.7% and hyposmia

in 21.8% of cases) versus 3.5% (6 cases of hyposmia) in the control group (*P* < .001). Normal olfactory function was detected in 73.5% of cases and 96.5% of controls. The Sniffin' Sticks score in the COVID-19 group was significantly lower than in the control group (32.5 [interquartile range, 29-36.5] versus 36.75 [34-39.5], *P* < .001; **Figure 1**). The prevalence of parosmia, phantosmia, and gustatory disturbances was significantly higher in subjects with previous SARS-CoV-2 infection. In the COVID-19 group, a significant correlation was found between lower TDI scores and female sex (odds ratio, 2.037 [95% CI, 1.246-4.213], *P* = .011).

Discussion

Only Boscolo-Rizzo et al¹³ have investigated the prevalence of self-reported POD in subjects at least 1 year after COVID-19, detecting a prevalence of 30.5%. In our study, 25.9% of patients self-reported some form of olfactory loss, while 26.5% revealed OD on psychophysical tests. This difference, while not seeming significant, contains within it the possible bias introduced by those patients who identified the presence of a purely qualitative disorder as “olfactory loss.” In contrast, some subjects with POD on psychophysical tests did not report any subjective dysfunction, due to overestimation of recovery.

The prevalence of OD found in the current study is in line with that reported by other authors at 6 months.^{3,6} This suggests that spontaneous recovery beyond 6 months may be limited; however, olfactory recovery has been reported many years after infection with other viruses,¹⁴ and our data should be considered intermediate findings.

As might therefore have been expected, the frequency of previously unrecognized olfactory disturbances in the control population was very low (3.5%) but also compatible with the

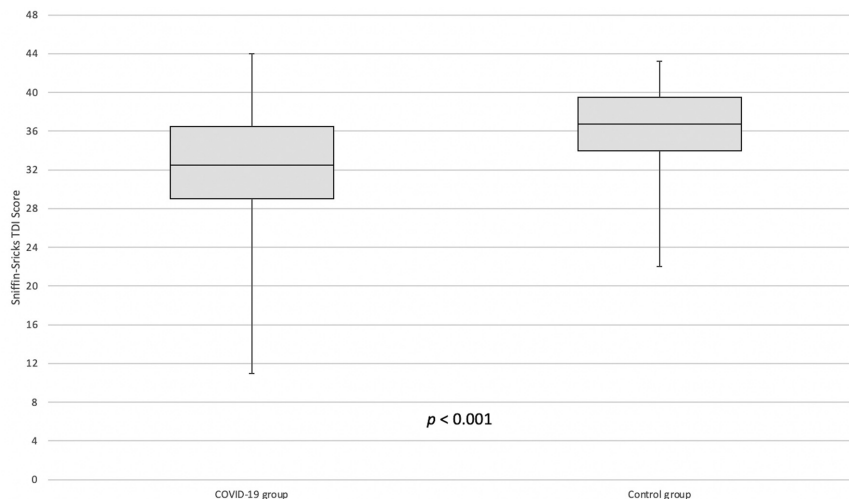


Figure 1. TDI scores in the 2 study groups. Values are presented as median (line), interquartile range (box), and 95% CI (error bars). TDI, threshold, discrimination, and identification.

relatively young average age of the recruited subjects. The differences in TDI scores and incidence of POD between the populations were statistically significant and refute the hypothesis that much of the prevalence of residual OD found in previous studies of COVID-19 is attributable to preexisting occult OD.⁸ Furthermore, a significant number of patients self-reported the presence of parosmia and phantosmia. This finding has important clinical implications, as qualitative disturbances of smell can reduce the quality of life of patients even more than merely quantitative ones.¹⁵

Several hypotheses have been proposed to explain such long-lasting OD, ranging from complete destruction of the olfactory epithelium¹⁶ to local immune factors¹⁷ and the persistence of the virus in olfactory structures after initial recovery.¹⁸ Similarly, risk factors for the persistence of OD have not yet been identified.¹⁹⁻²³ Different from any other long-term follow-up study,^{5,6,8} female sex had a significant association with persistence of OD.

Conclusions

In this 1-year follow-up study, the prevalence of OD was significantly higher in the COVID-19 group than in the age-matched control group. This finding supports initial indications that the growing number of patients with POD will be an unprecedented challenge for health care systems, and it highlights the importance of developing effective therapies to prevent and treat POD in patients with COVID-19.

Authors Contributions

Luigi Angelo Vaira, conceptualization of the work, development of the methodology, data curation, writing the original draft, writing the final draft, final approval; **Giovanni Salzano**, development of the methodology, writing the original draft, final approval; **Serge Daniel Le Bon**, data collection, data curation, revision of the original and final draft, final approval; **Angelantonio Maglio**, data collection, data curation, revision of the original and final draft, final approval; **Marzia Petrocelli**, data collection, data

curation, revision of the original and final draft, final approval; **Younes Steffens**, data collection, data curation, revision of the original and final draft, final approval; **Enrica Ligas**, data collection, data curation, revision of the original and final draft, final approval; **Fabio Maglito**, data collection, data curation, revision of the original and final draft, final approval; **Jerome R. Lechien**, review of the literature, statistical analysis, review of the first draft, final approval; **Sven Saussez**, review of the literature, statistical analysis, review of the first and final draft, final approval; **Alessandro Vatrella**, provision of study instrumentation, development of the methodology, supervision, review of the first and final draft, final approval; **Francesco Antonio Salzano**, provision of study instrumentation, development of the methodology, supervision, review of the first and final draft, final approval; **Paolo Boscolo-Rizzo**, review the methodology, review of the first draft, writing of the final manuscript, final approval; **Claire Hopkins**, review the methodology, review of the first draft, writing of the final manuscript, final approval; **Giacomo De Riu**, conceptualization of the work, development of the methodology, data curation, writing the original draft, writing the final draft, final approval.


Disclosures

Competing interests: None.

Sponsorships: None.

Funding source: None.

ORCID iD

Luigi Angelo Vaira  <https://orcid.org/0000-0002-7789-145X>

References

1. Lechien JR, Chiesa-Estomba CM, Beckers E, et al. Prevalence and 6-month recovery of olfactory dysfunction: a multicentre study of 1363 COVID-19 patients. *J Intern Med*. 2021;290:451-461.
2. Otte MS, Bork ML, Zimmermann PH, Flussmann JP, Luers JC. Persisting olfactory dysfunction improves in patients 6 months after COVID-19 disease. *Acta Otolaryngol*. 2021;141:626-629.

3. Riestra-Ayora J, Yanes-Diaz J, Esteban-Sanchez J, et al. Long-term follow-up of olfactory and gustatory dysfunction in COVID-19: 6 months case-control study un health workers. *Eur Arch Otorhinolaryngol*. 2021;278(12):4831-4837. doi:10.1007/s00405-021-06764-y
4. Lucidi D, Molinari G, Silvestri M, et al. Patient-reported olfactory recovery after SARS-CoV-2 infection: a 6-month follow-up study. *Int Forum Allergy Rhinol*. 2021;11:1249-1252.
5. 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. doi:10.1093/chemse/bjab006
6. 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;135:436-441.
7. 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;59:26-31.
8. Niklassen AS, Draf J, Huat C, et al. COVID-19: recovery from chemosensory dysfunction. A multicentre study on smell and taste. *Laryngoscope*. 2021;131:1095-1100.
9. Oleszkiewicz A, Schriever VA, Croy I, Hahner A, Hummel T. Updated Sniffin' Sticks normative data based on an extended sample of 9139 subjects. *Eur Arch Otorhinolaryngol*. 2019;276:719-718.
10. Hannum ME, Ramirez VA, Lipson SJ, et al. Objective sensory testing methods reveal a higher prevalence of olfactory loss in COVID-10-positive patients compared to subjective methods: a systematic review and meta-analysis. *Chem Senses*. 2020;45:865-874.
11. 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;28:419-422.
12. Rumeau C, Nguyen DT, Jankowski R. How to assess olfactory performance with the Sniffin' Sticks test. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2016;133:203-206.
13. 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*. Published online May 7, 2021. doi:10.1007/s00405-021-06839
14. Cavazzana A, Larsson M, Munch M, Hahner A, Hummel T. Postinfectious olfactory loss: a retrospective study on 791 patients. *Laryngoscope*. 2018;128:10-15.
15. Croy I, Nordin S, Hummel T. Olfactory disorders and quality of life—an updated review. *Chem Senses*. 2014;39:185-194.
16. Vaira LA, Hopkins C, Sandison A, et al. Olfactory epithelium histopathological findings in long-term coronavirus disease 2019 related anosmia. *J Laryngol Otol*. 2020;134:1123-1127.
17. Saussez S, Sharma S, Thiriard A, et al. Predictive factors of smell recovery in a clinical series of 288 coronavirus disease 2019 patients with olfactory dysfunction. *Eur J Neurol*. 2021;28(11):3702-3711. doi:10.1111/ene.14994
18. Dias De Melo G, Lazarini F, Levallois S, et al. COVID-19-related anosmia is associated with viral persistence and inflammation in human olfactory epithelium and brain infection in hamsters. *Sci Transl Med*. 2021;13:eabf8396.
19. Vaira LA, Deiana G, Lechien JR, et al. Correlations between olfactory psychophysical scores and SARS-CoV-2 viral load in COVID-19 patients. *Laryngoscope*. 2021;131(10):2312-2318. doi:10.1002/lary.29777
20. Vaira LA, De Vito A, Deiana G, et al. Systemic inflammatory markers and psychophysical olfactory scores in coronavirus disease 2019 patients: is there any correlation? *J Laryngol Otol*. 2021;135:723-728.
21. Vaira LA, De Vito A, Deiana G, et al. Correlations between IL-6 serum level and olfactory dysfunction severity in COVID-19 patients: a preliminary study. *Eur Arch Otorhinolaryngol*. Published online May 13, 2021. doi:10.1007/s00405-021-06868-5
22. Amadu AM, Vaira LA, Lechien JR, Scaglione M, Saba L, Lampus ML. Analysis of the correlations between the severity of lung involvement and olfactory psychophysical scores in coronavirus disease 2019 (COVID-19) patients. *Int Forum Allergy Rhinol*. Published online July 22, 2021. doi:10.1002/alr.22869
23. Vaira LA, Hopkins C, Petrocelli M, et al. Smell and taste recovery in coronavirus disease 2019 patients: a 60-day objective and prospective study. *J Laryngol Otol*. 2020;134:703-709.