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SARS-CoV-2 Effects on Psychophysical Olfactory Scores: Prospective Study With Evaluation Before and 60-Days After Infection

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Abstract

The aim of this study was to prospectively evaluate the olfactory function in a series of individuals infected with SARS-CoV-2 and who had undergone psychophysical olfactory assessment prior to infection. Individuals unexposed to SARS-CoV-2 infection underwent a psychophysical evaluation of smell with the Sniffin' Sticks test. The subjects were followed prospectively and included in the study if they developed SARS-CoV-2 infection with a second test 60 days after recovery. At the 60-day follow-up of the 41 included subjects, 2 (4.9%) self-reported persistent olfactory dysfunction (OD). The differences between TDI scores before and after infection were statistically significant (37 [interquartile range (IQR), 34.25-39.25] vs 34.75 [IQR, 32.25-38]; $p = .021$). Analyzing the individual olfactory domains, the differences were significant for threshold (T) (9.75 [IQR, 9-11.25] vs 8.25 [IQR, 7.25-10.25]; $p = .009$) but not for odor discrimination (D) ($p = .443$) and identification (I) ($p = .159$). SARS-CoV-2 causes a significant reduction in the olfactory function, in particular affecting the olfactory threshold, even in subjects who do not self-report an OD.

Keywords

ageusia, anosmia, coronavirus, COVID-19, Maxillofacial Surgery, olfactory dysfunction, olfactory function, Omicron variant, prospective study, PS/QI, SARS-CoV-2, smell, taste, taste dysfunction

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The prevalence of olfactory dysfunction (OD) during and after COVID-19 has been the subject of numerous studies that reported reliable data based on psychophysical tests.[1-5] A common limitation of all these studies is the lack of an objective olfactory assessment prior to infection. For this reason, it has never been possible to understand exactly to what extent the SARS-CoV-2 infection impacted psychophysical scores or whether recovery was actually complete.

The aim of this study was to evaluate the recovery of olfactory function in a series of individuals for whom a psychophysical olfactory assessment was available prior to infection.

Materials and Methods

A control group of volunteers who had never had SARS-CoV-2 infection was recruited between January and February 2022 at the University Hospital of Sassari (ethical approval PG 2021/7118). The exclusion criteria were the following: previous OD, previous surgery, radiotherapy or trauma to the nasal cavity, chronic rhinosinusitis with and without nasal polyps, and neurological or psychiatric comorbidities. All individuals underwent psychophysical olfactory evaluation by means of the extended version of the Sniffin' sticks test (SST)[6,7] evaluating 3 domains of the olfactory function: threshold (T), odor discrimination (D), and identification (I).

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All controls were asked to inform researchers if they developed SARS-CoV-2 infection in the period following this first evaluation. During the infection, the presence of OD was investigated using the specific item of the COVID-19 symptom index.[8] At least 60 days after the infection, all the patients underwent a second psychophysical evaluation.

Differences between baseline and postinfection TDI scores were analyzed with the Wilcoxon test (statistical significance set at $p < .05$).

Results

One hundred twenty subjects were included in the control group. Between February and April 2022, 41 of these (21 men, 20 women, mean age 41 ± 7.6 years; vaccination rate: 100%) developed SARS-CoV-2 infection. Prior to infection, the 41 individuals had a median TDI score of 37 (interquartile range [IQR], 34.25-39.25). Olfactory function was normal in 39 cases while hyposmia was detected in 2 cases (**Table 1**).

During the infection, 7 patients (17.1%) self-reported OD (4 cases of hyposmia and 3 cases of anosmia).

At the 60-day follow-up, 2 individuals (4.9%) self-reported persistent OD. At the SST, a median TDI score of 34.75 (IQR, 32.25-38) was detected with 4 cases of hyposmia; in 2 of them, OD was already present at baseline. The differences between TDI scores before and after infection were statistically significant (37 [IQR, 34.25-39.25] vs 34.75 [IQR, 32.25-38]; $p = .021$). Analyzing the individual olfactory domains, the differences were significant for T (9.75 [IQR, 9-11.25] vs 8.25 [IQR, 7.25-10.25]; $p = .009$) but not for D (13 [IQR, 12-14] vs 13 [IQR, 12-14]; $p = .443$) and I (14 [IQR, 13-14] vs 13 [IQR, 12-14]; $p = .159$) (**Figure 1**).

Discussion

The present study was carried out when the Omicron variant had a prevalence greater than 98%,[9] the prevalence of self-reported OD during infection is, therefore, lower than the previous variants[1,10] but in line with what was reported for Omicron.[11,12] In addition, all subjects who developed COVID-19 were previously vaccinated, and this may further reduce the risk of OD.[13]

To date, there are no studies on the recovery of olfactory function in individuals infected with the Omicron variant but these partial data at 60 days suggest a rate of persistent OD lower than that reported for the previous variants.[14,15] The timing of the second evaluation was established on the basis of the duration of the regeneration cycle of the olfactory epithelium (OE), which should be completed in 30 days.[16] At the 60-day follow-up, subjects reported a significantly lower TDI score compared to baseline although, in almost all cases, patients did not self-report an OD. The reduction was mainly due to a significant impairment of threshold, while discrimination and identification were intact. It has been suggested that this may be linked to a reduction in the number of receptors on the OE.[17] The recovery of discrimination and identification would be consistent with the presence of an intact olfactory pathway without alterations of higher cognitive processes. This pattern is also typical of OD from sinonasal disease.[18]

The results of this study suggest that SARS-CoV-2 induces damage to the OE that may be not perceived by patients. Although an unconscious alteration of the sense of smell may not impact the quality of life, it can expose people to environmental hazards.[19,20]

Some authors have hypothesized that the ability of the Omicron variant to infect the supporting cells of the OE is reduced due to a lower affinity of the spike protein with TMPRSS2 receptors[21] and also possibly due to a more effective local immunity in vaccinated subjects.[22] However, this study demonstrates that this ability is certainly not abolished and that the onset of OD is probably a more complex interplay of viral replication and inflammatory response. Olfactory training has proved particularly effective in improving olfactory scores and, in particular, in lowering the threshold.[23,24] Considering the absence of side effects, it could be indicated to suggest olfactory rehabilitation to all infected even if they do not self-report an OD.

The primary limitation was the small size of the cohort. Although all controls were subjected to regular swabs and immunoglobulin assays, which were consistently negative, previous undetected infections cannot be excluded.

Table 1. Olfactory Function Assessment Results

	Before the infection		During the infection		60 days after the infection	
Self-reported OD	*N*	% (95% confidence interval)	*N*	% (95% confidence interval)	*N*	% (95% confidence interval)
Normal	41	100% (91.4-100)	34	82.9% (67.9-92.8)	39	95.1% (83.5-99.4)
Hyposmia	0	0% (0-8.6)	4	9.8% (2.7-23.1)	2	4.9% (0.6-16.5)
Anosmia	0	0% (0-8.6)	3	7.3% (1.5-19.9)	0	0% (0-8.6)
TDI score	37 [IQR, 34.25-39.25]		Not available		34.75 [IQR, 32.25-38]	

TDI score classifies the olfactory function in normal (TDI score of ≥31), hyposmia (TDI score from 17 to 30.75), and anosmia (TDI score of <17).
Abbreviations: D, odor discrimination; I, identification; IQR, interquartile range; OD, olfactory dysfunction; T, threshold.

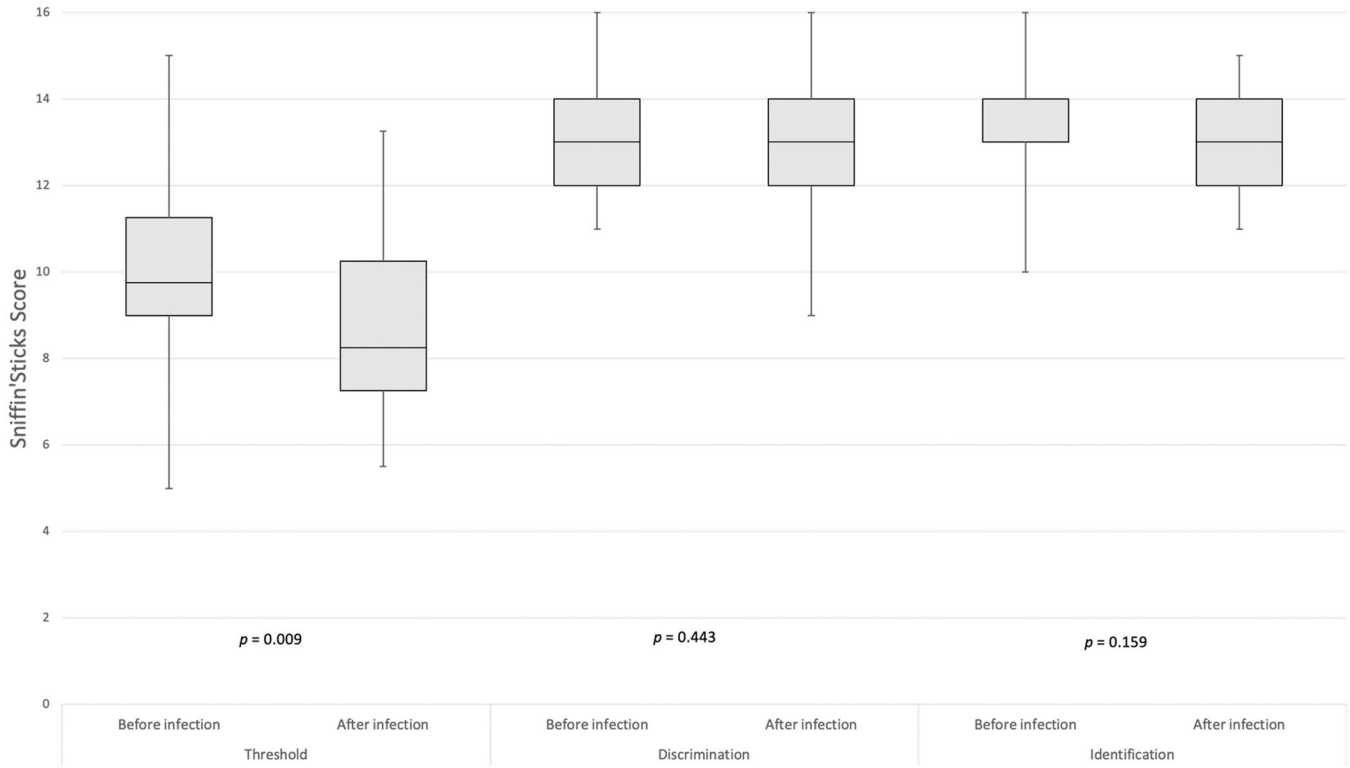

Figure 1. Comparison of olfactory scores before and after infection. Each olfactory subtest was assigned a score of 1-16 (for T) or between 0 and 16 (for D and I). D, odor discrimination; I, identification; T, threshold.

Second, the observation period is still too short and it cannot be excluded that there may be further improvements in the TDI score beyond 60 days.

Conclusions

SARS-CoV-2 causes a significant reduction in olfactory function, in particular with reduced threshold scores even in subjects who do not self-report smell loss.

Author Contributions

Luigi Angelo Vaira, conceptualization of the work, development of the methodology, data curation, writing the original draft, writing the final draft, final approval; **Jerome R. Lechien**, review of the literature, statistical analysis, review of the first draft, final approval; **Giovanni Salzano**, data collection, data curation, revision of the original end final draft, final approval; **Fabio Maglitto**, data collection, data curation, revision of the original end 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

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