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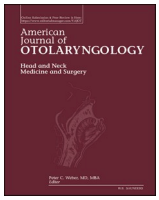

Recovery from olfactory and gustatory dysfunction following COVID-19 acquired during Omicron BA.1 wave in Italy☆

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ABSTRACT

Background: Despite alterations in the sense of smell and taste have dominated the symptoms of SARS-CoV-2 infection, the prevalence and the severity of self-reporting COVID-19 associated olfactory and gustatory dysfunction has dropped significantly with the advent of the Omicron BA.1 subvariant. However, data on the evolution of Omicron-related chemosensory impairment are still lacking.
Objective: The aim of the present study was to estimate the prevalence and the recovery rate of self-reported chemosensory dysfunction 6-month after SARS-CoV-2 infection acquired during the predominance of the Omicron BA.1 subvariant in Italy.
Methods: Prospective observational study based on the sino-nasal outcome tool 22 (SNOT-22), item "sense of smell or taste" and additional outcomes conducted in University hospitals and tertiary referral centers in Italy.
Results: Of 338 patients with mild-to-moderate COVID-19 completing the baseline survey, 294 (87.0 %) responded to the 6-month follow-up interview. Among them, 101 (34.4 %) and 4 (1.4 %) reported an altered sense of smell or taste at baseline and at 6 months, respectively. Among the 101 patients with COVID-19-associated smell or taste dysfunction during the acute phase of the disease, 97 (96.0 %) reported complete resolution at 6 months. The duration of smell or taste impairment was significantly shorter in vaccinated patients ($p = 0.007$).
Conclusions: Compared with that observed in subjects infected during the first wave of the pandemic, the recovery rate from chemosensory dysfunctions reported in the present series of patients infected during the predominance of the Omicron BA.1 subvariant was more favorable with a shorter duration being positively influenced by vaccination.

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1. Introduction

From the outbreak of the COVID-19 pandemic to the emergence of the delta variant, alterations in the sense of smell and taste have dominated the symptoms of SARS-CoV-2 infection [1–4]. Moreover, chemosensory dysfunction was among the most common symptoms complained by COVID-19 long haulers, significantly impacting on the quality of life [5–7].

Since January 17, 2022, Omicron variant was by far the most predominant variant in Italy with an overall prevalence of 96 % [8]. Particularly, in Friuli Venezia-Giulia and Sardinia, the prevalence of SARS-CoV-2 infection driven by Omicron variant was 97.0 % and 96.2 %, respectively [8]. The advent of Omicron lineages have considerably changed the clinical presentation of the disease, with the most significant differences being the lesser involvement of the lower respiratory tract and the reduced probability of hospital admission and mortality [9,10].

The lower severity of COVID-19 was ascribed to both the different biological and immunopathological properties of Omicron and its subvariants and the higher prevalence of vaccinated subjects during the circulation of this variant [11,12]. Real-world data have shown that people who are vaccinated may still get COVID-19 but they are much less likely to experience severe outcomes than people who are unvaccinated [13].

In a series of Italian subjects who developed a mild-to-moderate COVID-19, we have previously observed that both the prevalence and the severity of self-reporting COVID-19 associated smell and taste dysfunction has dropped significantly with the advent of the Omicron BA.1 subvariant [14]. These observations were then confirmed in a large mobile-app-based observational study [9]. However, data on the evolution of Omicron-related chemosensory dysfunction are still lacking.

The aim of the present study was to estimate the prevalence and the recovery rate of self-reported chemosensory dysfunction at the 6-month follow-up in the same cohort of patients.

2. Materials and methods

Informed consent was obtained for telephone interviews. This is a prospective study on mild-to-moderate symptomatic adult patients resident in Friuli Venezia Giulia and Sardinia, who tested positive for SARS-CoV-2 RNA by polymerase chain reaction (PCR) on nasopharyngeal swabs performed according to World Health Organization recommendation since January 17 [15]. Subjects were considered mild if they had symptoms of COVID-19 without shortness of breath, dyspnea, or abnormal chest imaging. COVID-19 was instead considered as moderate if there was evidence of lower respiratory disease during clinical assessment or imaging and the oxygen saturation was ≥94 % [16]. Patients did not require hospitalization and therefore were considered suitable for being treated at home.

The contacts of home-isolated subjects with a confirmed diagnosis of COVID-19 were provided by the prevention departments of the hospitals involved. To be included in study, patients had to have: (1) age ≥ 18 years, (2) PCR-confirmed SARS-CoV-2 infection in accordance with World Health Organization recommendation, (3) mild to moderate illness that could be managed in home isolation, (4) a SARS-CoV-2 infection acquired since January 17, 2022. The exclusion criteria were: (1) contact information not available, (2) uncooperative patients, (3) assisted ventilation, (4) psychiatric or neurological disorders, (5) previous surgery or radiotherapy in the oral and nasal cavities, (6) preexisting self-reported smell and taste dysfunction, (7) history of head trauma, (8) allergic rhinitis, and (9) chronic rhinosinusitis. The subjects were contacted by telephone by the researchers and interviewed.

The following information were collected for each patient: gender, age, smoking and alcohol drinking habits and comorbidities (immunosuppression, diabetes, obesity, cardiovascular or pulmonary disease, cancer, renal or hepatic failure), date of first positive and negative swab, vaccination status.

During the acute phase of the disease and 6 months later, in all the patients symptoms were assessed through the same standardized questions and structured questionnaires, as previously described [14], and including the Sino-Nasal Outcome test 22 (SNOT-22), item “sense of smell or taste” as previously reported. The SNOT-22 ranks symptom severity as none (0), very mild (1), mild or slight (2), moderate (3), severe (4), or as bad as it can be (5). Patients with SNOT-22 ≥ 1 were also asked, based on a binary outcome of yes and no, whether the chemosensory dysfunction involved the sense of smell, taste, or both. Patients were asked about SARS-CoV-2 vaccination status, including number of doses. Individuals were considered fully vaccinated if they had received both doses of a two-dose vaccine schedule at least 14 days before symptom onset, or one dose of a single-dose vaccine schedule at least 28 days before symptom onset. At the follow-up interview, patients were asked about the duration (days) of the smell and taste dysfunction.

Symptom prevalence was expressed as percentage of total patients, and 95 % confidence interval (CI) were calculated using Clopper-Pearson method. The risk of chemosensory impairment persistence, expressed as odds ratio (OR), was estimated through unconditional logistic regression model. Variables which were significant at the univariate analysis with a type I error < 0.10 were further included in the multivariable model. Duration of chemosensory impairment was express in days; differences across strata were evaluated through Mann-Whitney test. The independent associations of type of chemosensory impairment and vaccination on duration were evaluated non-parametric analysis of variance (ANOVA). Analyses were performed using R 3.6. and statistical significance was claimed for $p < 0.05$ (two-tailed).

3. Results

Of 482 potential eligible patients developing mild-to-moderate COVID-19 in the period from January 17, 2022, to February 4, 2022, 144 did not respond or declined to take part in the survey leaving a total of 338 completing the baseline interview. Of 338 patients with mild-to-moderate SARS-Co2-2 infection completing the baseline survey, 294 (87.0 %) responded to the 6-month follow-up interview (median [range] age, 46 [21–83] years; 163 [55.4 %] women). Patients' characteristics are shown in Table 1.

Among them, 101 (34.4 %, 95 % CI: 28.9–40.1 %) and 4 (1.4 %, 0.4–3.4 %) reported an altered sense of smell or taste (SNOT-22 > 0) at baseline and 6-months, respectively (Table 2). Among the 101 patients with the onset of COVID-19-associated smell or taste dysfunction, 97 (96.0 %, 95 % CI: 90.2–98.9 %) reported complete resolution at 6 months, 2 (2.0 %, 95 % CI: 0.2–7.0 %) reported a decrease in the severity, and 2 (2.0 %, 95 % CI: 0.2–7.0 %) reported the symptom worse. Seven patients, all fully vaccinated, had reinfection at a median of 156 days (range, 106–181) from the first infection. Three of these reported a rapidly resolving alteration in the sense of smell at the time of the first infection. None of them complained of persistent changes in smell at the time of reinfection that was not accompanied by an onset of chemosensory changes in all seven cases.

No socio-demographic characteristics were associated with the onset of smell or taste dysfunction during COVID-19 (Supplementary Table). Conversely, the duration of chemosensory impairment was significantly and independently shorter in vaccinated patients versus those with no or incomplete vaccination (median duration: 6 versus 8 days; $p = 0.007$) and in those complained an isolated smell or taste dysfunction versus both dysfunctions at the same time (median duration: 4 versus 7 days; $p = 0.045$) (see Fig. 1). Chemosensory impairment shorter than 7 days was associated with younger age, alcohol drinking, and full vaccination (Table 3), though the risk was still significant in the multivariable model only for full vaccination (OR = 0.26; 96 % CI: 0.08–0.89).

Table 1
Baseline characteristics of 294 symptomatic COVID-19 patients infected with SARS-CoV-2 Omicron variant.

	n	%	(95 % CI)[a]
Gender			
Female	163	55.4	(49.6–61.2)
Male	131	44.6	(38.8–50.4)
Age (years)			
Median (Q1-Q3)	46	34–60	
Body mass index (kg/m^2)			
<25	171	58.2	(52.3–63.9)
25 to <30	86	29.3	(24.1–34.8)
≥30	37	12.6	(9.0–16.9)
Tobacco smoking			
Never	180	61.2	(55.4–66.8)
Ever	114	38.8	(33.1–44.6)
Alcohol drinking			
Never	214	72.8	(67.3–77.8)
Ever[b]	80	27.2	(22.2-32.7)
Number of comorbidities			
0	195	66.3	(60.0–71.7)
1	57	19.4	(15.9–24.4)
2	22	7.5	(4.7–11.1)
≥3	20	6.8	(4.2–10.3)
Vaccination			
Non-vaccinated or partially vaccinated	50	17.0	(12.9–21.8)
Fully vaccinated	244	83.0	(78.2–87.1)
Two doses	128	52.5	(46.0–58.9)
Three doses	116	47.5	(41.1–54.0)

[a] 95 % CIs were calculated using Clopper-Pearson method.
[b] For men, consuming >4 drinks on any day or >14 drinks per week; for women, consuming >3 drinks on any day or >7 drinks per week.

Table 2
Evolution of symptoms at six months from Omicron SARS-CoV-2 infection in 294 COVID-19 patients.

	Acute phase			6-Month follow-up		
	n	%	(95 % CI)[a]	n	%	(95 % CI)
Chemosensory impairment (SNOT-22 ≥ 1)						
Yes	101	34.4	(28.9–40.1)	4	1.4	(0.4–3.4)
No	193	65.6	(59.9–71.1)	290	98.6	(96.6–99.6)
Type of chemosensory impairment						
Smell & taste	67	22.8	(18.1–28.0)	3	1.0	(0.2–3.0)
Only smell	16	5.4	(3.1–8.7)	1	0.3	(0.0–1.9)
Only taste	18	6.1	(3.7–9.5)	0	0.0	(0.0–1.2)
Severity of alteration of sense of smell or taste (SNOT-22)						
0 = None	193	65.6	(59.9–71.1)	290	98.6	(96.6–99.6)
1 = Very mild	20	6.8	(4.2–10.3)	0	0.0	(0.0–1.2)
2 = Mild/slight	25	8.5	(5.6–12.3)	2	0.7	(0.1–2.4)
3 = Moderate	25	8.5	(5.6–12.3)	1	0.3	(0.0–1.9)
4 = Severe	15	5.1	(2.9–8.3)	1	0.3	(0.0–1.9)
5 = As bad as it can be	16	5.4	(3.1–8.7)	0	0.0	(0.0–1.2)

Abbreviations: SNOT-22: Sino Nasal Outcome Test 22.

4. Discussion

We previously observed that the prevalence of smell or taste dysfunction during the Omicron period dropped from 63 % to 25 % and from 57 % to 27 %, respectively, when compared with the frequency observed during the pre-Omicron phase of the pandemic [14,17]. Moreover, the severity of the smell and taste dysfunction was lower in subjects infected during the predominance of the Omicron variant [14]. In the present study, we also found a very favorable evolution with a prevalence of persistent dysfunction of 1.4 % 6-month after SARS-CoV-2 infection acquired during the predominance of the Omicron BA.1 subvariant, reflecting a recovery rate of 96 %. These figures are better than those observed 6-months after infection with G614 variant when the complete recovery was self-reported by only 44–70 % of cases [7]. This finding was also confirmed by solid psychophysical studies reporting that prevalence and the recovery rate were 18 % and 70 %, respectively [18].

While the onset of chemosensory changes did not appear to be affected by the vaccination status, the duration of symptoms was significantly shorter in the vaccinated subjects. These findings suggest that both a different biology of the variant and vaccination may be responsible for the different landscape of the alterations in smell and taste observed in subjects infected since Omicron BA.1 subvariant became predominant. The Omicron variant of SARS-CoV-2 carries over 30 mutations in its spike protein which inefficiently uses the cellular protease TMPRSS2 [19]. This both compromises cell entry in TMPRSS2-expressing cells and syncytia formation which was supposed to be a pathogenic mechanism for COVID-19 related smell dysfunction [20]. Another support to the theory of minor pathogenicity is given by the recent study by Armando et al. [11] in which hamsters were infected with D614G and Gamma, Delta and Omicron variants. At the histopathological analysis of samples taken from the olfactory mucosa, the animals infected with the latter variant showed significantly less severe and widespread alterations than the previous variants.

Secretory IgA (sIgA), located on the mucous membranes may play a crucial role in mucosal immunity [21]. Vaccines delivered through the parenteral intramuscular route elicit primarily circulating antibodies [22]. However, recent studies provided evidence that both systemic and nasal/salivary mucosal sIgA responses are induced after SARS-CoV-2 mRNA vaccination [23,24] with mucosal humoral immune response being stronger after the injection of the second vaccine dose compared to subjects recovered from COVID-19 [24]. High levels of nasal IgA represent the only factor for which a positive correlation was found with the recovery of olfactory function after COVID-19 [25]. Such evidence provides mechanistic support to our observation of faster recovery of smell and taste dysfunction in vaccinated subjects.

Subjects with combined self-reported alterations in both sense of smell and taste had significantly longer recovery times regardless of vaccination status. A similar correlation between associated smell and taste loss during the infection and duration of olfactory dysfunction was found by Ferreli et al. [26] in a study conducted during the alpha variant period. It is well known that patients may self-report loss of taste when they develop loss of flavor perception because of an impairment in the retronasal olfactory function. Thus, some patients with isolated alteration of the sense of smell may have suffered less extensive damage to the olfactory neuroepithelium such as not to compromise the retronasal sense of smell and characterized by faster recovery times [27]. The isolated alteration of the sense of taste could depend in some cases on other factors such as drugs administered during the acute phase of the disease (e.g. NSAID or some kinds of antibiotic such as ciprofloxacin), so that these patients could have rapidly recovered from hypogeusia after drug discontinuation [28].

This study has the following limitations. First, symptoms were self-reported and based on telephone interview. These studies have several advantages: they were easy to be carried out, quick, and most importantly they have a baseline parameter of comparison that is, the subjective perception of smell preceding the onset of covid-19. However, it has been previously demonstrated that, compared with psychophysical evaluation, this approach is a source of important bias as it significantly underestimates the real prevalence and severity of the chemosensory dysfunction [29,30]. Particularly, patients tend to overestimate the recovery from olfactory dysfunction. Thus, a psychophysical evaluation is warranted to identify patients with an unconscious alteration of the sense of smell that could expose them to environmental risks. Second, patients were included in the study based on epidemiological data from

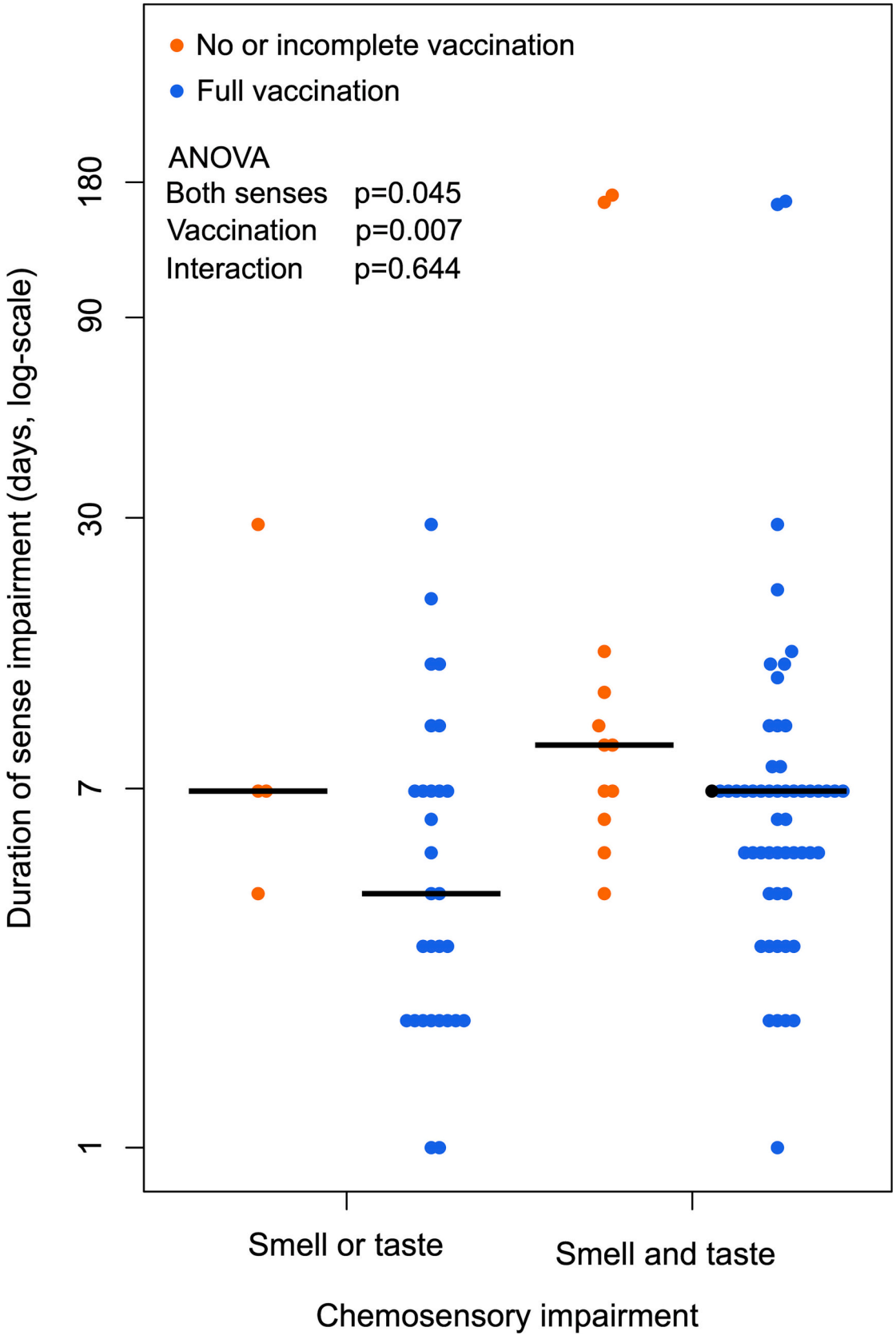

Fig. 1. Duration of impairment of sense of smell and test according to type of sense impairment and vaccination. Horizontal bars represent median values.

Table 3
Odds ratio (OR) and corresponding 95 % confidence intervals (CI)[a] for duration of chemosensory impairment >7 days according to socio-demographic and clinical characteristics.

	Duration of chemosensory impairment				Univariate	Multivariable
	≤7		>7			
	n	(%)	n	(%)	OR (95 % CI)	OR (95 % CI)
Gender						
Male	31	(77.5)	9	(22.5)	Reference	
Female	43	(70.5)	18	(29.5)	1.44 (0.57–3.63)	
Age (years)						
<35	25	(89.3)	3	(10.7)	Reference	Reference
35 to 54	33	(70.2)	14	(29.8)	3.53 (0.92–13.64)	2.88 (0.71–11.78)
≥55	16	(61.5)	10	(38.5)	5.21 (1.24–21.86)	4.37 (0.99–19.16)
Body mass index (kg/m^2)						
<25	44	(73.3)	16	(26.7)	Reference	
25 to <30	16	(69.6)	7	(30.4)	1.20 (0.42–3.46)	
≥30	14	(77.8)	4	(22.2)	0.79 (0.23–2.74)	
Tobacco smoking						
Never	44	(74.6)	15	(25.4)	Reference	
Ever	30	(71.4)	12	(28.6)	1.17 (0.48–2.86)	
Alcohol drinking						
Never	52	(68.4)	24	(31.5)	Reference	Reference
Ever	22	(88.0)	3	(12.0)	0.30 (0.08–1.08)	0.51 (0.11–2.29)
Number of comorbidities						
0–1	64	(76.2)	20	(23.8)	Reference	
≥2	10	(58.8)	7	(41.2)	2.24 (0.75–6.65)	
Vaccination						
Partially/unvaccinated	8	(50.0)	8	(50.0)	Reference	Reference
Fully vaccinated	66	(77.6)	19	(22.4)	0.30 (0.10–0.87)	0.26 (0.08–0.89)
SNOT22 at baseline						
1–3	53	(75.7)	17	(50.0)	Reference	
4–5	21	(67.7)	10	(32.3)	1.49 (0.59–3.76)	
Type of sense impairment						
One sense	27	(79.4)	7	(20.6)	Reference	
Both senses	47	(70.2)	20	(29.9)	1.64 (0.62–4.38)	

[a] Estimated from unconditional logistic regression model.

small samples sequenced regionally and we unable to estimate to what extent the sample was contaminated by non-Omicron cases. However, to reduce this bias, we decided to limit the analysis to cases of SARS-CoV-2 infection diagnosed when the Omicron variant was estimated to be above 95 %. Third, limitations of the study also include the response rate: even if patients were contacted consecutively from lists provided by the Department of Prevention and were not told the primary purpose of the study, it is possible that patients with more severe symptoms were more likely to participate in the study. Similarly, it is possible that patients with persistent symptoms were more inclined to undergo re-evaluation by introducing a selection bias. Fourth, patients were asked to self-report the duration of chemosensory disturbances and this finding may be subject to recall bias.

5. Conclusion

The prevalence at the onset, severity and persistence of chemosensory dysfunction at 6-months were lower in patients infected during the predominance of the Omicron BA.1 subvariant. Although it does not reduce the prevalence rate, vaccination appears to reduce the recovery time. Both the virologic characteristics of the variant and a previous vaccination could be responsible for the changed characteristics of post-COVID-19 chemosensory dysfunction. However, about 1.5 % of the subjects still complained a persistent smell and taste dysfunction 6-month after the infection. Considering the higher transmissible of the Omicron variant [31], this may continue to significantly feed the pool of subjects with long-term chemosensory dysfunctions. Vaccination could reduce the duration of non-life-threatening but highly distressing symptoms of long-COVID-19. Further investigations are needed to evaluate any differences in the rates and characteristics of olfactory and gustatory dysfunction in subjects infected by other circulating Omicron subvariants.

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Ethics committee approval

The study was approved by the Ethics Committees of the Friuli Venezia Giulia Region (CEUR-OS156) and University Hospital of Cagliari (PG 2021/7118).

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CRediT authorship contribution statement

Paolo Boscolo-Rizzo: concept and design, acquisition, analysis, or interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and supervision; **Giancarlo Tirelli**: interpretation of data, critical revision of the manuscript for important intellectual content, and supervision; **Pierluigi Meloni**: interpretation of data, critical revision of the manuscript for important intellectual content, and supervision; **Claire Hopkins**: interpretation of data, critical revision of the manuscript for important intellectual content, and supervision; **Jerome R. Lechien**: interpretation of data, critical revision of the manuscript for important intellectual content, and supervision; **Giordano Madeddu**: acquisition, analysis, or interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content; **Pierluigi Bonini**: acquisition, analysis, or interpretation of data, critical revision of the manuscript for important intellectual content; **Nicoletta Gardenal**: acquisition, analysis, or interpretation of data, critical revision of the manuscript for

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Declaration of competing interest

The Authors declare that there is no conflict of interest.

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