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ORIGINAL ARTICLE

Coronavirus disease 2019 (COVID-19)–related smell and taste impairment with widespread diffusion of severe acute respiratory syndrome–coronavirus-2 (SARS-CoV-2) Omicron variant

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Abstract

Background: The aim of this study was to estimate the prevalence of self-reported chemosensory dysfunction in a study cohort of subjects who developed a mild-to-moderate coronavirus disease 2019 (COVID-19) in the period from January 17, 2022, to February 4, 2022 (Omicron proxy period) and compared that with a historical series of patients testing positive for severe acute respiratory syndrome–coronavirus-2 (SARS-CoV-2) infection between March and April, 2020 (comparator period).

Methods: Prospective study based on the 22-item Sino-Nasal Outcome Tool (SNOT-22), item "sense of smell or taste" and additional outcomes.

Results: Patients' characteristics and clinical presentations of COVID-19 were evaluated and compared in 779 patients, 338 of the study cohort and 441 of the historical series. The prevalence of self-reported chemosensory dysfunction during the proxy Omicron period (32.5%; 95% confidence interval [CI], 27.6–37.8) was significantly lower from that during the comparator period (66.9%; 95% CI, 62.3–71.3) ($p < 0.001$). Nearly one-quarter of patients (24.6%; 95% CI, 20.1–29.5) reported an altered sense of smell during the proxy Omicron period compared to 62.6% (95% CI, 57.9–67.1) during the comparator period ($p < 0.001$). Similarly, the prevalence of an altered sense of taste dropped to 26.9% (95% CI, 22.3–32.0) during the proxy Omicron period from 57.4% (95% CI, 52.6–62.0) during the comparator period ($p < 0.001$). The severity of chemosensory dysfunction was lower in the proxy Omicron period compared to the comparator period ($p < 0.001$).
Conclusion: The prevalence and the severity of COVID-19–associated smell and taste dysfunction has dropped significantly with the advent of the Omicron variant but it still remains above 30%.

KEYWORDS
COVID-19, olfactory dysfunction, Omicron variant, SARS-CoV-2, smell, taste

1 | INTRODUCTION

In December 2021, the World Health Organization (WHO) defined five severe acute respiratory coronavirus 2 (SARS-CoV-2) variants of concern (VOC): Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2 and AY lineages), and Omicron (originally B.1.1.529, then reclassified into BA lineages).[1] The Omicron variant, first detected in South Africa on October 24, 2021, represents the most recently recognized VOC.[2] Compared to Delta, which was the most prevalent variant worldwide in December 2021, Omicron spread more rapidly, becoming the dominant variant in January 2022.[3]

Omicron seems to cause a less severe disease with determinants of severity being multifactorial and including a lower replication competence in the lung parenchyma compared to bronchus.[4] Consistently, the spectrum of symptoms is expected to differ from that observed in the coronavirus disease 2019 (COVID-19) driven by other SARS-CoV-2 strains. However, to the best of our knowledge, only one report has been published so far regarding the prevalence of different symptoms in infections driven by this VOC.[5]

Smell and taste dysfunction were consistently reported among the most common symptoms of COVID-19 with about 65%–70% of patients with mild-to-moderate disease experiencing a chemosensory impairment during the acute phase of the COVID-19.[6–8] Recently, in a series of 81 subjects tested positive for the SARS-CoV-2 Omicron variant, the impairment of the sense of smell and taste was self-reported by 12% and 23% of patients, respectively.[5] Since January 17, 2022, the Omicron variant was by far the most predominant variant in Italy, with an overall prevalence of 95.8%.[9] Particularly, in Friuli Venezia-Giulia and Sardinia, the prevalence of SARS-CoV-2 infection driven by the Omicron variant was 97.0% and 96.2%, respectively.[9]

The aim of this study was to determinate the prevalence of self-reported chemosensory dysfunction in a series of Italian subjects who developed a mild-to-moderate COVID-19 after January 17, 2022, and to compare it with that of a cohort of patients who tested positive for SARS-CoV-2 infection and were evaluated during the first wave of the pandemic in Italy.

2 | PATIENTS AND METHODS

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

2.1 | Subjects

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 WHO recommendations between January 17 and February 4, 2022.[10] Consecutive contacts of subjects with a confirmed diagnosis of SARS-CoV-2 infection were identified by the hospitals involved. Patients were considered mildly-to-moderately symptomatic if they had less severe clinical symptoms with no evidence of pneumonia, not requiring hospitalization, and therefore considered suitable for being treated at home. Participants had to be interviewed within 1 month of the first positive swab. To be included in the study, subjects had to be recovered from the infection with a negative PCR confirmation on the nasopharyngeal swab or have had remission of symptoms for at least 7 days. The exclusion criteria were as follows: contact information not available, uncooperative patients, assisted ventilation, psychiatric or neurological disorders, previous surgery or radiotherapy in the oral and nasal cavities, preexisting self-reported smell and taste dysfunction, history of head trauma, allergic rhinitis, and chronic rhinosinusitis. The subjects were contacted by telephone by the researchers and interviewed.

2.2 | Questionnaires

Telephone interview were conducted between January 28 and February 14, 2022. Demographic and clinical data were collected through standardized questions administered during the interview including gender, age, self-reported height and weight, smoking habit, and the following comorbidities: immunosuppression, diabetes, cardiovascular diseases, active cancer, chronic respiratory disease, kidney disease, liver disease. Obesity was defined as having a body mass index (BMI) of ≥30. Symptoms were assessed through standardized questions and structured questionnaires, including the Acute Respiratory Tract Infection Questionnaire (ARTIQ; with symptoms scored as none, 0; a little, 1; a lot, 2) and the 22-item Sino-Nasal Outcome Test (SNOT-22), item "sense of smell or taste" as previously reported.[6] 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. Then, patients were asked whether their gustatory alteration involved the perception of basic taste ("Do you have an impairment in the perception of fine taste, e.g., during eating and drinking?") or flavor ("Do you have an impairment in the perception your basic taste: sweet, sour, salty, bitter?"). The dates of the first positive and negative swabs were obtained. In addition, patients were asked if they had already been infected with SARS-CoV-2 since the beginning of the pandemic and if they had been vaccinated and with how many doses. Individuals were considered fully vaccinated if they had received the required dose(s) of a SARS-CoV-2 vaccine and were at least 14 days after completion.

2.3 | Statistical analysis

We compared demographic and clinical data, with special emphasis on chemosensory dysfunction, for patients who developed COVID-19 in the period from January 17, 2022 to February 4, 2022 in Italy (Omicron proxy period), with an historical cohort of patients who completed the same outcomes prospectively, resident in the same Italian regions, who developed COVID-19 between March and April, 2020,[11–14] when the G614 variant[15] was dominant (comparator period). Symptom prevalence was expressed as percentage of total patients, and 95% confidence intervals (CIs) were calculated using the Clopper-Pearson method. Differences in prevalence were evaluated through Fisher's exact test and odds ratios (ORs) for variables associated for chemosensory dysfunction were calculated according to multivariable unconditional logistic regression model adjusted for age and gender. Analyses were performed using R 3.6 and statistical significance was claimed for $p < 0.05$ (two-tailed). When presenting results from both cohorts the proxy Omicron cohort data is presented first throughout the manuscript, followed by the comparator group.

3 | RESULTS

The study included 779 patients, 338 from the study cohort (proxy Omicron period) and 441 from the historical cohort (comparator period).

3.1 | Characteristics of the proxy omicron period cohort

Of 482 potential eligible patients, 144 did not respond or declined to take part in the survey leaving a total of 338 (70.1%; median [IQR] age 46 [34–59] years; 183 [54%] women) who participated in the study. Patients' characteristics are reported in Table 1. Associated comorbidities were reported by 116 subjects (34.3%), with the most common being cardiovascular diseases reported by 56 patients (16.6%). A total of 279 patients (82.5%) reported that they had been fully vaccinated for SARS-CoV-2. Eighteen patients (5.3%) reported having already contracted a SARS-CoV-2 infection during the previous 2 years. Most frequent symptoms were blocked nose (68.3%), fever (58.9%), and

TABLE 1 Baseline characteristics of patients with mild-to-moderate COVID-19 during the proxy Omicron period versus comparator period

Characteristic	Proxy Omicron period ($n = 338$)		Comparator period ($n = 441$)		p
	n	Prevalence % (95% CI)[a]	n	Prevalence % (95% CI)[a]	
Age, years (median, range)		46 (34–59)		50 (39–58)	0.160
Sex					0.885
Male	155	45.9 (40.5–51.3)	199	45.1 (40.4–31.4)	
Female	183	54.1 (48.7–559.5)	242	54.9 (50.1–59.6)	
Smoking status					0.335
Never	200	59.2 (53.7–64.5)	277	62.8 (58.1–67.3)	
Ever	138	40.8 (35.5–46.3)	164	37.2 (32.7–41.9)	
Current alcohol drinking					<0.001
No	245	72.4 (67.4–77.2)	238	54.0 (49.2–58.7)	
Yes	93	27.5 (22.8–32.6)	203	46.0 (41.3–50.8)	
Comorbidity					
None	222	65.7 (60.4–70.7)	297	67.3 (62.8–71.7)	0.008
1	68	20.1 (16.0–25.0)	110	24.9 (21.0–29.3)	
≥2	48	14.2 (10.7–18.4)	34	7.7 (5.4–10.6)	
Specific comorbidities					
Immunosuppression	13	3.8 (2.1–6.5)	22	5.0 (3.2–7.5)	0.489
Diabetes mellitus	20	5.9 (3.7–9.0)	22	5.0 (3.2–7.5)	0.632
Obesity	30	8.9 (6.1–12.4)	55	12.5 (9.5–15.9)	0.132
Cardiovascular disease	56	16.6 (12.8–21.0)	41	9.3 (6.8–12.4)	0.003
Malignancy	12	3.6 (1.8–6.1)	12	2.7 (1.4–4.7)	0.536
Chronic respiratory diseases	28	8.3 (5.6–11.8)	23	5.2 (3.3–7.7)	0.107
Kidney failure	18	5.3 (3.2–8.3)	9	2.0 (0.9–3.8)	0.017
Liver disease	16	4.7 (2.7–7.6)	5	1.1 (0.4–2.6)	0.003
Vaccination status prior to infection					
Fully vaccinated[b]	266	78.7 (73.9–82.9)		NA	
Partially vaccinated	23	6.8 (4.4–10.0)		NA	
Non-vaccinated	49	14.5 (10.9–18.7)		NA	

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; NA, not applicable; SARS-CoV-2, severe acute respiratory syndrome–coronavirus-2.
[a]95% CIs were calculated using the Clopper-Pearson method.
[b]Individuals were considered fully vaccinated if they had received the required dose(s) of a SARS-CoV-2 vaccine and were at least 14 days past completion.

dry cough (56.8%) (Table 2). Alterations of sense of smell or taste were reported by 110 patients (32.5%; 95% CI, 27.6–37.8), with 61 patients reporting a SNOT-22 > 2 (18.0; 95% CI, 14.1–22.6). Eighteen patients (5.3%) reported a score of 5 (Table 2). When asked about basic taste and flavor perception, 72 (21.3%) and 87 (25.7%) patients, respectively, self-reported an impairment with 68 (20.1%) subjects reporting both (data not shown).

3.2 | Differences in clinical presentation comparing the two periods

The study cohort was compared with an historical cohort of 441 patients who developed SARS-CoV-2 infection between March and April, 2020 (comparator period). The two cohorts showed similar distribution by gender, age, and smoking status. Approximately one-third of patients reported comorbidities in both periods (34.3% in the proxy Omicron period and 32.7% in the comparator period). However, multimorbidity was more frequent in the proxy Omicron period than in the comparator period (14.2% vs. 7.7%, $p = 0.008$). Cardiovascular disease was significantly most frequent in the Omicron period (16.6% vs. 9.3%, $p = 0.003$).

Significant differences in the prevalence of symptoms between the two periods were observed (Table 2). Particularly, blocked nose (68.3% vs. 26.3%; $p < 0.001$), dry cough (56.8% vs. 45.1%; $p = 0.002$), headache (55.0% vs. 45.4%; $p = 0.005$), sore throat (50.9% vs. 25.6%; $p < 0.001$), coughing up mucus (26.0% vs. 12.7%; $p < 0.001$), and sinonasal pain (20.1% vs. 12.2%; $p = 0.004$) were more common in the

TABLE 2 Characteristics and prevalent symptoms in patients with mild-to-moderate COVID-19 during the proxy Omicron period versus comparator period

Characteristic	Proxy Omicron period ($n = 338$)		Comparator period ($n = 441$)		
	n	Prevalence % (95% CI)[a]	*n*	Prevalence % (95% CI)[a]	*p*
Symptoms based on the ARTIQ[b]					
Dry cough	192	56.8 (51.3–62.2)	199	45.1 (40.4–49.9)	0.002
Coughing up mucus	88	26.0 (21.4–31.1)	56	12.7 (9.7–16.2)	<0.001
Blocked nose	231	68.3 (63.1–73.3)	116	26.3 (22.2–30.7)	<0.001
Fever	199	58.9 (53.4–64.2)	295	66.9 (62.3–71.2)	0.024
Headache	186	55.0 (49.6–60.4)	200	45.4 (40.6–50.1)	0.005
Sore throat	172	50.9 (45.4–56.3)	113	25.6 (21.6–30.0)	<0.001
Muscle pain	173	51.2 (45.7–56.6)	223	50.6 (45.8–55.3)	0.885
Joint pain	151	44.7 (39.3–50.1)	217	49.2 (44.4–54.0)	0.219
Chest pain	72	21.3 (17.1–26.1)	92	20.9 (17.2–25.0)	0.929
Sinonasal pain	68	20.1 (16.0–24.8)	54	12.2 (9.3–15.7)	0.004
Loss of appetite	96	28.4 (23.7–33.5)	176	39.9 (35.3–44.6)	<0.001
Problems breathing	79	23.3 (19.0–28.3)	102	23.1 (19.3–27.4)	0.932
Wheezing	48	14.2 (10.7–18.4)	57	12.9 (9.9–16.4)	0.672
Shortness of breath	92	27.2 (22.5–32.3)	138	31.3 (27.0–35.8)	0.235
Felt tired	241	71.3 (66.2–76.1)	301	68.3 (63.7–72.6)	0.388
Other symptoms					
Red eyes	27	8.0 (5.3–11.4)	71	16.1 (12.8–19.9)	<0.001
Diarrhea	70	20.7 (16.5–25.4)	158	35.8 (31.3–40.5)	<0.001
Nausea	63	18.6 (14.6–23.2)	80	18.1 (14.7–22.1)	0.926
Vomiting	15	4.4 (2.5–7.2)	27	6.1 (4.1–8.8)	0.339
Abdominal pain	53	153.7 (12.0–20.0)	54	12.2 (9.3–15.7)	0.174
Insomnia	62	18.3 (14.4–22.9)	100	22.7 (18.8–26.9)	0.154
Dizziness	37	10.9 (7.8–14.8)	55	12.5 (9.5–15.9)	0.576
Chemosensory impairment (SNOT-22 ≥ 1)					<0.001
Yes	110	32.5 (27.6–37.8)	295	66.9 (62.3–71.3)	
No	228	67.5 (62.2–72.4)	146	33.1 (28.7–37.7)	
Type of chemosensory impairment					
Smell	83	24.6 (20.1–29.5)	276	62.6 (57.9–67.1)	<0.001
Taste	91	26.9 (22.3–32.0)	253	57.4 (52.6–62.0)	<0.001
Smell and taste	65	19.2 (15.2–23.8)	234	53.1 (48.3–57.8)	<0.001
Only smell	18	5.3 (3.2–8.3)	42	9.5 (7.0–12.7)	0.003
Only taste	26	7.7 (5.1–11.1)	19	4.3 (2.6–6.6)	0.371
Severity of alteration of sense of smell or taste (SNOT-22)					
0 = None	228	67.5 (62.2–72.4)	146	33.1 (28.7–37.7)	<0.001
1 = Very mild	21	6.2 (3.9–9.3)	7	1.6 (0.6–3.2)	
2 = Mild/light	28	8.3 (5.6–11.8)	35	7.9 (5.6–10.9)	
3 = Moderate	27	8.0 (5.3–11.4)	48	10.9 (8.1–14.2)	
4 = Severe	16	4.7 (2.7–7.6)	64	14.5 (11.4–18.2)	
5 = As bad as it can be	18	5.3 (3.2–8.3)	141	32.0 (27.6–36.5)	

Abbreviations: ARTIQ, acute respiratory tract infection questionnaire; CI, confidence interval; COVID-19, coronavirus disease 2019; SNOT-22, 22-item Sino-Nasal Outcome Test.

[a]95% CIs were calculated using the Clopper-Pearson method.

[b]Prevalence is combined response of "a little" or "a lot."

proxy Omicron period, whereas loss of appetite, diarrhea, and red eyes were significantly reported more frequently in the comparator period (Table 2).

The prevalence of self-reported chemosensory dysfunction during the proxy Omicron period (32.5%) was significantly lower from that during the comparator period (66.9%) ($p < 0.001$). Almost one-quarter (24.6%) of patients reported an altered sense of smell during the proxy Omicron period compared to 62.6% during the comparator period ($p < 0.001$). Similarly, the prevalence of an altered sense of taste dropped to 26.9% during the proxy Omicron period, from 57.4% during the comparator period ($p < 0.001$). Moreover, the severity of chemosensory dysfunction, as measured by SNOT-22 score, was significantly lower in the proxy Omicron period compared to the comparator period ($p < 0.001$).

3.3 | Variables associated with chemosensory dysfunction

None of the tested variables emerged as significantly associated with chemosensory alteration in patients who contracted the infection during the proxy Omicron period (Supplementary Table). Vaccination status was not predictive of the chemosensory outcome, with 33.3% and 32.3% of fully-vaccinated and partially-vaccinated/unvaccinated subjects, respectively, self-reporting a SNOT-22 ≥ 1 ($p = 0.888$). Although nasal obstruction was present in more than two-thirds of patients, the prevalence of smell dysfunction in patients with and without nasal obstruction was 25.1% (58/173) and 24.3% (26/81), respectively ($p = 1.000$).

4 | DISCUSSION

We observed a statistically significant reduction in the prevalence of smell and taste alterations in patients who developed the disease during the proxy Omicron period compared to that observed in patients who contracted SARS-CoV-2 infection during the comparator period, with the prevalence of smell and taste dysfunction dropping from 63% to 25% and from 57% to 27%, respectively.

One of the possible reasons for this difference is the modulation that the vaccine may have had on clinical expression of SARS-CoV-2 infection. Indeed, vaccination has amply demonstrated its effectiveness in making the clinical manifestations of COVID-19 less severe.[16,17] However, in the present series the prevalence of chemosensory dysfunction was not influenced by the vaccination status. Furthermore, a vaccination effect on the prevalence of chemosensory disorders does not appear to be supported by several other observations. Current vaccines against SARS-CoV-2 are based on systemic injection that predominantly induces production of circulatory immunoglobulin G (IgG) and, potentially, cytotoxic T cells, which are poorly effective at generating mucosal immune responses; that is, secretory IgA.[18] Therefore, the olfactory neuroepithelium appears theoretically still vulnerable to SARS-CoV-2 even in vaccinated patients. Early studies found no significant correlation between serum immunoglobulin levels and duration of olfactory disfunction.[19,20] The correlation is instead significant with nasal immunoglobulin.[20] Also, vaccination was demonstrated to be less effective against the highly mutated Omicron variant[21] and the data of the present analysis support this: even patients who received the booster dose developed a symptomatic disease. Finally, we previously observed that chemosensory dysfunctions were among the most frequent symptoms of COVID-19 in vaccinated subjects when the pandemic was mainly driven by the Delta variant.[22]

The Omicron variant is a highly mutated strain of SARS-CoV-2, showing many substitutions in the spike glycoprotein, which may impact on the affinity for the angiotensin converting enzyme 2 (ACE-2) receptor. It has been shown that the supporting cells as well as horizontal basal cells and globose basal of the olfactory neuroepithelium are targeted by SARS-CoV-2.[23,24] Both of these cell populations display the molecular makeup that makes these cells prone to SARS-CoV-2 infection, that is, ACE2 receptor and transmembrane serine protease 2 (TMPRSS2), which are, conversely, not expressed by the olfactory sensory neurons.[23,24] Recent experimental observations support the fact that the Omicron variant has an unique mechanism of cellular entry which shifted cell trophism from TMPRSS2-expressing cells.[25] Thus, a different interaction between the virus and cellular targets may be responsible for the reduction in the chemosensory impairment observed during the proxy Omicron period.

Smell and taste impairment were consistently described as pathognomonic manifestations of COVID-19, with several studies confirming the high sensitivity and specificity of self-reported new onset of smell and/or taste impairment for COVID-19 in populations of patients with flu-like symptoms.[26–28] It is very likely that the advent of Omicron may deprive us of this differential diagnosis tool and that COVID-19, at least in its mild-moderate form, can easily be confused with other respiratory infections. Furthermore, symptoms of upper airway involvement, that is, blocked nose, sore throat, and coughing up mucus, were predominant in patients of the proxy Omicron period and quite more frequent than what observed in patients infected during the first wave of the pandemic.

Regarding the pathogenesis of the alteration of smell, conductive loss was thought not to play a major role in the

underlying mechanism, given the relatively lower prevalence of obstruction. Instead, damage to the supporting cells of the olfactory epithelium leading to indirect injury to the olfactory sensory neurons,[29] and downregulation of receptor expression are thought to be more important as the underlying mechanism of olfactory loss.[30] The higher prevalence of nasal obstruction and the lesser severity of the chemosensory dysfunction observed in the study cohort suggests that at least in part a conductive loss blocking inspired odorants from reaching the olfactory cleft in the nasal cavity could be a possible cause of the loss of smell in patients infected by the Omicron variant, perhaps with sparing of injury to the olfactory epithelium itself.[31,32] Further work will be required to test this hypothesis.

The high prevalence of COVID-19–associated chemosensory dysfunction observed in these last 2 years was unprecedented. The fall in prevalence of these disorders observed with the advent of the Omicron variant should not induce national health services to reduce the resources allocated to the diagnosis and treatment of smell and taste alterations because one-third of the infected still manifest chemosensitive dysfunctions. There are, indeed, a very large number of patients with long-term COVID-19 dominated by chemosensory alterations,[14,33] with important implications on the quality of life of these subjects.[33,34] Moreover, even if the prevalence of chemosensory disorders caused by the Omicron variant appears reduced, the greater spread of the virus can still lead to a significant number of patients with alterations in smell or taste. It will be of paramount importance to collect data relating to the evolution of Omicron-related chemosensory disorders, that is, recovery and persistence rate, to fully estimate the burden of chemosensory dysfunction caused by the SARS-CoV-2 Omicron variant.

Finally, the higher prevalence of patients with cardiovascular, hepatic, renal disease, and multimorbidity observed in the study cohort may be due to the lower aggressiveness of the Omicron variant,[35] where patients with these comorbidities tended to develop severe COVID-19 when infected by other SARS-CoV-2 strains.[36]

This study has the following limitations. First, hospitalized patients were not included in the study. Although this made our cohort more homogeneous, studies evaluating the impact of chemosensory dysfunction in more severe Omicron-driven COVID-19 are needed. Symptoms were self-reported and based on telephone interview. Although we tried to perform a comprehensive symptoms assessment, some symptoms may have been undetected. Furthermore, a more precise evaluation of the chemosensory function by psychophysical assessment was lacking. Another limitation may be the heterogeneity in the vaccine status across participants. Some of them having one dose of vaccine, whereas others completed the three doses at different times before the conduction of the study. Response bias may lead to an overestimation of the prevalence of olfactory dysfunction, although this may apply to both time periods. Ultimately, patient inclusion in the proxy Omicron period was based on epidemiological data from small samples sequenced regionally. We are therefore unable to estimate to what extent the sample is contaminated by non-Omicron cases. However, to reduce this bias, we decided to limit the analysis to cases of SARS-CoV-2 infection diagnosed after January 17, 2022, when the Omicron variant was estimated to be >95%.

5 | CONCLUSION

The prevalence and the severity of COVID-19–associated smell and taste dysfunction has dropped significantly with the advent of the Omicron variant but it still remains >30%. Although nasal obstruction was a symptom observed more frequently in the study cohort, the prevalence of chemosensory changes was similar in subjects with and without blocked noses, suggesting that a conductive loss may be the cause of the disturbance only in a fraction of cases. Studying the evolution of chemosensory loss will be of critical importance in assessing the burden of chemosensory dysfunction caused by the SARS-CoV-2 Omicron variant.

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[Correction added on 16 May 2022, after first online publication: CRUI funding statement has been added.]

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article.

AUTHOR CONTRIBUTIONS

Paolo Boscolo-Rizzo and Luigi Angelo Vaira had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Paolo Boscolo-Rizzo and Luigi Angelo Vaira. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Paolo Boscolo-Rizzo and Luigi Angelo Vaira. Critical revision of the manuscript for important intellectual content:

All authors. Statistical analysis: Jerry Polesel. Supervision: Paolo Boscolo-Rizzo, Giancarlo Tirelli, Claire Hopkins, Jerome R. Lechien, Giacomo De Riu, Luigi Angelo Vaira.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Tracking SARS-CoV-2 variants. World Health Organization. 2022. Accessed March 18, 2022. https://www.who.int/health-topics/typhoid/tracking-SARS-CoV-2-variants
2. Callaway E. Heavily mutated Omicron variant puts scientists on alert. *Nature*. 2021;600(7887):21.
3. Suzuki R, Yamasoba D, Kimura I, et al. Attenuated fusogenicity and pathogenicity of SARS-CoV-2 Omicron variant. *Nature*. Published online February 1, 2022. https://doi.org/10.1038/s41486-022-04462-1
4. Hui KPY, Ho JCW, Cheung M-C, et al. SARS-CoV-2 Omicron variant replication in human bronchus and lung ex vivo. *Nature*. Published online February 1, 2022. https://doi.org/10.1038/s41586-022-04479-6
5. Brandal LT, MacDonald E, Veneti L, et al. Outbreak caused by the SARS-CoV-2 Omicron variant in Norway, November to December 2021. *Euro Surveill*. 2021;26:2101147.
6. Spinato G, Fabbris C, Polesel J, et al. Alterations in smell or taste in mildly symptomatic outpatients with SARS-CoV-2 infection. *JAMA*. 2020;323:2089–2090.
7. Lechien JR, Chiesa-Estomba CM, Place S, et al. Clinical and epidemiological characteristics of 1,420 European patients with mild-to-moderate coronavirus disease 2019. *J Intern Med*. 2020;288:335–344.
8. 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.
9. [*Press Release N ° 08/2022 - Covid-19, flash survey Iss: 95.8% of Omicron positive samples on 17 January*]. Istituto Superiore di Sanità. Accessed March 18, 2022. https://old.iss.it/documents/20126/0/report_Flash_surveyVarianti_17+gennaio+2022.pdf/daa6af2a-3670-3757-bcba-651042081c4f?t=1643624975322
10. Technical guidance. World Health Organization. Accessed March 18, 2020. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance
11. 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.
12. Vaira LA, Hopkins C, Salzano G, et al. Olfactory and gustatory function impairment in COVID-19 patients: Italian objective multicenter-study. *Head Neck*. 2020;42:1560–1569.
13. Vaira LA, Lechien JR, Khalife M, et al. Psychophysical evaluation of the olfactory function: European Multicenter Study on 774 COVID-19 patients. *Pathogens*. 2021;10:62.
14. Boscolo-Rizzo P, Guida F, Polesel J, et al. Sequelae in adults at 12 months after mild-to-moderate coronavirus disease 2019 (COVID-19). *Int Forum Allergy Rhinol*. 2021;11:1685–1688.
15. Korber B, Fischer WM, Gnanakaran S, et al. Tracking changes in SARS-CoV-2 spike: evidence that D614G increases infectivity of the COVID-19 virus. *Cell*. 2020;182:812–827.e19.
16. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. *BMJ*. 2021;373:n1088.
17. Thompson MG, Burgess JL, Naleway AL, et al. Prevention and attenuation of Covid-19 with the BNT162b2 and mRNA-1273 vaccines. *N Engl J Med*. 2021;385:320–329.
18. Russell MW, Moldoveanu Z, Ogra PL, et al. Mucosal immunity in COVID-19: a neglected but critical aspect of SARS-CoV-2 infection. *Front Immunol*. 2020;11:611337.
19. Maiorano E, Calastri A, Robotti C, et al. Clinical, virological and immunological evolution of the olfactory and gustatory dysfunction in COVID-19. *Am J Otolaryngol*. 2022;43:103170.
20. 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;28:3702–3711.
21. Collie S, Champion J, Moultrie H, et al. Effectiveness of BNT162b2 vaccine against Omicron variant in South Africa. *N Engl J Med*. 2022;386:494–496.
22. Vaira LA, De Vito A, Lechien JR, et al. New onset of smell and taste loss are common findings also in patients with symptomatic COVID-19 after complete vaccination. *Laryngoscope*. 2022;132:419–421.
23. Gupta K, Mohanty SK, Mittal A, et al. The cellular basis of loss of smell in 2019-nCoV-infected individuals. *Brief Bioinform*. 2021;22:873–881.
24. Lechien JR, Radulesco T, Calvo-Henriquez C, et al. ACE2 & TMPRSS2 expressions in head & neck tissues: a systematic review. *Head Neck Pathol*. 2021;15:225–235.
25. Meng B, Abdullahi A, Ferreira IATM, et al. Altered TMPRSS2 usage by SARS-CoV-2 omicron impacts tropism and fusogenicity. *Nature*. Published February 1, 2022. https://doi.org/10.1038/s41586-022-04474-x
26. Gerkin RC, Ohla K, Veldhuizen MG, et al. Recent smell loss is the best predictor of COVID-19 among individuals with recent respiratory symptoms. *Chem Senses*. 2021;46:bjaa081.
27. Yan CH, Faraji F, Prajapati DP, et al. Association of chemosensory dysfunction and Covid-19 in patients presenting with influenza-like symptoms. *Int Forum Allergy Rhinol*. 2020;10:806–813.
28. Boscolo-Rizzo P, Borsetto D, Hopkins C, et al. Challenges in interpreting the diagnostic performance of symptoms to predict COVID-19 status: the case of anosmia. *Int Forum Allergy Rhinol*. 2020;10:1113–1115.
29. Butowt R, Von Bartheld CS. Anosmia in COVID-19: underlying mechanisms and assessment of an olfactory route to brain infection. *Neuroscientist*. 2021;27:582–603.
30. Zazhytska M, Kodra A, Hoagland DA, et al. Non-cell-autonomous disruption of nuclear architecture as a potential cause of COVID-19-induced anosmia. *Cell*. 2022;185(6):1052–1064.e12. https://doi.org/10.1016/j.cell.2022.01.024
31. Kahn M, Yoo SJ, Clijsters M, et al. Visualizing in deceased COVID-19 patients how SARS-CoV-2 attacks the respiratory and olfactory mucosae but spares the olfactory bulb. *Cell*. 2021;184:5932–5949.e15.

32. 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.
33. Vaira LA, Salzano G, Le Bon SD, et al. Prevalence of persistent olfactory disorders in patients with COVID-19: a psychophysical case-control study with 1-year follow-up. *Otolaryngol Head Neck Surg*. Published online November 23, 2021. https://doi.org/10.1177/01945998211061511
34. 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;59:517–527.
35. Bojkova D, Widera M, Ciesek S, et al. Reduced interferon antagonism but similar drug sensitivity in Omicron variant compared to Delta variant of SARS-CoV-2 isolates. *Cell Res*. 2022;32:319–321.
36. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054–1062.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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