Smell and taste alterations in COVID-19: a cross-sectional analysis of different cohorts

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Background: **Olfactory (OD) and gustatory (GD) dysfunction have been proven to be a typical symptom of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection. However, their prevalence in different patient populations still needs to be clarified.**

Methods: **A cross-sectional study was performed from March 27 to April 1, 2020, in Northern Italy. Physicians administered a survey-based questionnaire to SARS-CoV-2–positive patients with the aim of assessing symptoms, focusing on OD and GD. Two groups were studied: group A, patients hospitalized at Azianda Socio Sanitaria Territoriale (ASST) Spedali Civili University Hospital of Brescia; and group B, home-quarantined subjects.**

Results: **A total of 508 patients were enrolled: 295 in group A and 213 in group B. Mean age ± standard deviation (SD) was 55 ± 15 years; 56% were men. Overall, OD and GD were present in 56% (95% confidence interval [CI], 51% to 60%) and 63% (95% CI, 59% to 67%) of cases, respectively. In group A, the prevalence of OD and GD was 44% (95% CI, 38% to 50%) and 52% (95% CI, 46% to 58%), respectively. In group B, the prevalence of OD and GD was 72% (95% CI, 65% to 79%) and 79% (95% CI, 73% to 84%), respectively. In the entire cohort, total loss of olfaction and taste was reported in 64% and 60% of cases, respectively. OD and GD occurred as the first symptom in 10% and 11% of cases, respectively; in the remaining cases, they occurred after a mean of 4 ± 3 days following the first symptom. At the time of the questionnaire, complete resolution of OD and GD was reported in 52% and 55% of cases, respectively (mean duration, 9 ± 5 days in both).**

Conclusion: **OD and GD are more prevalent in home-quarantined subjects, and they are independently associated with younger age and female gender.** © 2020 ARS-AAOA, LLC.

Key Words:
COVID-19; SARS-CoV-2; olfactory dysfunction; gustatory dysfunction; smell; taste

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Since December 2019, the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) pandemic has been placing significant burden on healthcare systems and governments. Countries have applied a wide range of large-scale infection control policies to respond to the crisis, with variable results. Notwithstanding, these policies should be adaptive and evolve according to appropriate evidence.

In this view, 2 peculiarities of SARS-CoV-2 should be underlined. Different from SARS-CoV-1, SARS-CoV-2 is mainly localized in the upper airways and significant viral

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load levels are detectable in both asymptomatic and symptomatic patients.[1,2] These features are expected to cause a higher rate of upper airway complaints, and suggests a potential risk of transmission from asymptomatic and mildly symptomatic subjects. In fact, undocumented but infectious cases are a critical epidemiological issue and play a vital role in the transmission dynamics of SARS-CoV-2,[3] leading to the strong need to better identify this subgroup of subjects.

Recent reports on coronavirus disease 2019 (COVID-19) have highlighted a high prevalence of olfactory (OD) and gustatory dysfunction (GD).[4-7] OD in SARS-CoV-2–infected subjects has also been demonstrated with olfactometric tests,[7] and was independently associated with outpatient care in a recent study by Yan et al.[8]

In this view, the precise definition of highly specific symptoms may greatly improve the identification of undocumented subjects. However, screening policies should take into account the variability of these symptoms according to the characteristics of different patient populations.

The study aims to estimate the different characteristics of OD and GD in hospitalized patients and home-quarantined subjects with a nasal/pharyngeal swab positive for SARS-CoV-2 in an epidemic area.

Patients and methods

Study population, setting, and data collection

Cases with confirmed infection for SARS-CoV-2 were included in a cross-sectional study. Only laboratory-confirmed cases (positive by real-time polymerase chain reaction [RT-PCR] on a nasal/pharyngeal swab) were included. Serology was not available at the time of the study. Data were collected from March 27 to April 1, 2020, through a survey-based questionnaire on symptoms, focusing on OD and GD (ie, time of onset, duration, severity, characteristics, and relationship with other symptoms). This report followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[9]

Inclusion criteria were as follows:

- Signed written informed consent;
- Male or female >18 years of age;
- Willing and able to participate in the study;
- Positive nasal/pharyngeal swab for SARS-CoV-2 (RT-PCR);

Exclusion criteria were as follows:

- Legal incapacity or limited legal capacity;
- Medical or psychological condition or situation which in the opinion of the investigator would not Permit the patient to complete the questionnaire or sign informed consent;
- Invasive ventilation;
- Noninvasive ventilation preventing adequate communication;
- Preexisting chronic anosmia and/or ageusia.

Enrolled cases included:

- Group A: patients hospitalized in COVID-19 Units (Pneumology, Internal Medicine, Infectious Disease, and Emergency) of the ASST Spedali Civili University Hospital (Brescia, Italy);
- Group B: home-quarantined subjects recruited through exponential snowball sampling. Each subject provided the contact information of confirmed positive cases in his/her social circle. After specific consent, positivity to nasal/pharyngeal swab for SARS-CoV-2 was confirmed through access to their clinical data or contact with their general practitioner.

Healthcare system policy for nasal/pharyngeal swab for SARS-CoV-2 were defined as: recent (less than 14 days) close contact (<1 m for >15 minutes and without personal protective equipment) with someone who tested positive for SARS-CoV-2 and symptoms highly suggestive for COVID-19. The test was repeated within 24 to 48 hours in case of negative results and persistent suspicious symptoms.

All subjects with positive nasal/pharyngeal swab for SARS-CoV-2 were home-quarantined or hospitalized. Factors evaluated for hospitalization included:

- Severe or worsening symptoms;
- Partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FIO_2) <350 or PaO_2 <75 mm of mercury (Hg) or blood oxygen saturation (SaO_2) <94%;
- Unfavorable home and social conditions;
- Evidence of moderate/severe interstitial pneumonia at chest X-ray, chest computed tomography (CT), or chest ultrasound;
- Age >65 years;
- Presence of significant comorbidities.

The indication for hospitalization or quarantine was considered as a surrogate marker of full-blown disease (group A) or mildly symptomatic clinical presentation (group B), respectively.

Patients were not informed about the specific study aim to minimize confirmation bias. All subjects signed an informed consent form approved by the institutional review board. The study was performed following the principles of the Declaration of Helsinki and was approved by the Research Review Board, Ethics Committee, of the ASST Spedali Civili of Brescia, Italy (study reference number: NP4037).

Study objectives

The primary objective was the estimate of prevalence and definition of timing of onset, resolution, and characteristics of OD and GD in COVID-19 hospitalized and home-quarantined subjects. The secondary objective was the assessment of the association of OD/GD with patient

characteristics, symptoms, and radiological pulmonary alterations.

Study definitions

Hereinafter, when we refer to our cohort, we intend all individuals included in the study (group A+B) as "cases," those hospitalized (group A) as "patients," and those home-quarantined (group B) as "subjects."

Coexisting conditions were ascertained from physician documentation and questionnaire administration. Symptoms presenting as a consequence of a known pharmacological side effect or oxygen therapy were excluded from evaluation.

Chest X-ray was performed in all hospitalized patients (group A). Since March 4, 2020, in our hospital a chest X-ray scoring system was introduced for semiquantitative assessment of lung disease in COVID-19. It ranked the pulmonary involvement on a 0 to 18-point severity scale (18 being the most severe) according to the extent and characteristics of lung infiltrates.[10]

Specimen collection and testing

Clinical samples for SARS-CoV-2 diagnostic testing were obtained according to World Health Organization (WHO) guidelines.[11] The nasal/pharyngeal swab was performed using UTM® COPAN FLOQSwabs® (COPAN, Murrieta, CA). SARS-CoV-2 nucleic acids were detected by RT-PCR using GeneFinder™ COVID-19 Plus RealAmp Kit by OSANG Healthcare (Anyang, Republic of Korea), or Allplex™ 2019-nCoV Assay by Seegene Inc. (Seoul, Republic of Korea). The 2 kits have comparable diagnostic accuracy.

Survey-based questionnaire

The survey-based questionnaire was precisely defined and administered by a physician. The translated version of the questionnaire and data collection form is described in the Supporting Information. Data were collected in a dedicated database.

Statistical analysis

On the basis of an expected OD prevalence of 30%, we estimated that given a maximum risk of type I error of 5%, a sample size of 500 patients would provide an estimate with a precision plus or minus 4%.

The prevalence of OD, GD, and their corresponding 95% confidence intervals (CIs) were calculated according to binomial distributions. The tetrachoric correlation between OD and GD was also calculated. Comparisons between group A and B were performed using *t* test, Mann-Whitney, and chi-square tests as appropriate. Multivariable logistic regression models were used to assess factors related to OD and GD, while a multivariable linear regression model was performed to evaluate factors associated with radiologic score. Results were expressed in terms of odds ratios (ORs) and regression coefficients, respectively. The final models included factors associated with outcomes when adjusting for age (bivariable analyses). For more details, see the Supporting Information.

Results

Demographic and clinical characteristics

A total of 575 cases were evaluated; of those, 508 were included in the study. Fifty-six patients were excluded due to critical health conditions (ie, irresponsive, unconscious, and with significant respiratory effort), 6 due to preexisting chronic ageusia or anosmia (5 undocumented and 1 due to total laryngectomy), 3 due to language barrier, and 2 refused to participate in the study.

Group A included 295 (58%) hospitalized patients and group B was composed of 213 (42%) home-quarantined subjects. Mean ± standard deviation (SD) lag time between swab and survey, and between symptoms onset and survey was 11 ± 8 days and 18 ± 7 days, respectively (Table 1). The mean ± SD age was 55 ± 15 years (range, 18–91 years); 56% were men. In all, 40% of cases had no significant comorbidity. Group A had a significantly higher prevalence of older patients, smokers, and comorbidities. Cohort characteristics by group are summarized in Table 1, Supporting Table 1, and Supporting Table 2.

Prevalence

The prevalence of symptoms is detailed in Table 2. In the entire population, OD and GD were present in 56% (95% CI, 51% to 60%) and 63% (95% CI, 59% to 67%) of cases, respectively. In group A the prevalence of OD and GD was 44% (95% CI, 38% to 50%) and 52% (95% CI, 46% to 58%), respectively. Their prevalence was significantly higher in group B: 72% (95% CI, 65% to 78%) and 79% (95% CI, 73% to 84%), respectively. OD and GD were more prevalent in younger patients, females, nonsmokers, and those without comorbidities (Table 3). OD and GD were reported as complete loss (anosmia or ageusia) in 64% and 60% of cases, respectively. GD without OD was present in 10% of cases.

Onset and duration

OD and GD developed at the onset in 10% and 11% of cases, respectively; in 5% they were the only complaint. The remaining developed the symptom after a mean of 4 ± 3 days. At the time of the questionnaire, complete resolution of OD and GD was reported by 56% and 59% of cases, respectively, with a similar mean duration (9 ± 5 days) (Table 4).

Associations at multivariable analysis

At multivariable analyses, older age (10-year age increase; OR 0.76; 95% CI; 0.67 to 0.87; $p < 0.001$) and male gender (OR 0.62; 95% CI, 0.43 to 0.91; $p = 0.015$) were associated with a decreased risk of OD; whereas

TABLE 1. Demographic and clinical characteristics*

Variable	Hospitalized (Group A) (n = 295)	Home-quarantined (Group B) (n = 213)	*p* (Group A vs B)
Age (years), mean ± SD (range)	61.9 ± 12.8 (24–91)	44.7 ± 12.1 (18–74)	<0.001
Gender, n (%)			
Male	204 (69.2)	81 (38.0)	<0.001
Female	91 (30.8)	132 (62.0)	
History of smoking, n (%)			
Nonsmoker	184 (62.4)	158 (74.2)	<0.001
Current smoker [average py]	12 (4.1) [29.4 py]	18 (8.4) [7.3 py]	
Former smoker [average py]	99 (33.5) [25.4 py]	37 (17.4) [15.7 py]	
Lag time from swab to survey (days), mean ± SD (range)	6.9 ± 6.1 (1–39)	16.2 ± 7.9 (0–35)	<0.001
Lag time from onset of symptoms to survey, mean ± SD (range)	15.9 ± 6.7 (1–45)	20.9 ± 7.4 (6–45)	<0.001
Major comorbidities, n (%)			
Obesity	60 (20.3)	7 (3.3)	<0.001
Hypertension	140 (47.5)	26 (12.2)	<0.001
Cardiac disease	48 (16.3)	4 (1.9)	<0.001
Diabetes mellitus	59 (20)	6 (2.8)	<0.001
Renal disease	11 (3.7)	1 (0.5)	0.017
Chronic or allergic rhinosinusitis/asthma	27 (9.2)	26 (12.2)	0.267
Pulmonary disease	21 (7.1)	2 (0.9)	0.001
Immunodeficiency[a]	26 (8.8)	5 (2.3)	0.005
Others[b]	59 (11.6)	29 (5.7)	0.011
Comorbidities, n (%)			
None	63 (21.3)	142 (66.7)	<0.001
1–2	176 (59.7)	62 (29.1)	
>2	56 (19.0)	9 (4.2)	

*Statistical tests were used as appropriate (*t* test, Mann-Whitney test, chi-squared test).
[a]Immunodeficiency includes immunosuppressive therapy, recent or current hematological malignancy.
[b]Other comorbidities include history of cancer, hypothyroidism, chronic neurological conditions, liver and vascular diseases.
py = pack-year; SD = standard deviation.

arthromyalgia (OR 1.76; 95% CI, 1.21 to 2.57; $p = 0.003$) and nasal congestion (OR 1.62; 95% CI, 1.01 to 2.6; $p = 0.047$) with an increased risk. Similar results were found considering GD, demonstrating a negative association with age (OR 0.78; 95% CI, 0.68 to 0.89; $p < 0.001$) and male gender (OR 0.89; 95% CI, 0.33 to 0.72; $p < 0.001$), and a positive association with arthromyalgia (OR 1.85; 95% CI, 1.25 to 2.73; $p = 0.002$) (Supporting Table 3). No evidence of association between OD/GD and the radiologic score was observed (analysis limited to group A) (Supporting Information).

By network analysis, a strong positive connection was detected between OD and GD. Other solid connections were found between diarrhea and nausea, fever and arthromyalgia, and nasal congestion and pharyngodynia (Fig. 1, Supporting Fig. 1).

Discussion

The study describes a sample of more than 500 cases with confirmed SARS-CoV-2 infection, distinguishing between hospitalized patients and home-quarantined subjects. Overall, the prevalence of OD and GD was over 50%. In accordance with recent evidence,[8] in our series both symptoms had a significantly higher prevalence in home-quarantined subjects (72% and 79%, respectively). These prevalence rates are in line with 2 recent cross-sectional studies, in which the prevalence of OD and GD was 68%

TABLE 2. Prevalence of symptoms in the series

Symptom, n (%)	Hospitalized (Group A) (n = 295) n (%)		Home-quarantined (Group B) (n = 213) n (%)		*p* (Group A vs B) (chi-squared test)
	Total	First symptom	Total	First symptom	
Olfactory dysfunction	130 (44.1)	34 (11.5)	153 (71.8)	18 (8.5)	<0.001
Gustatory dysfunction	153 (51.9)	35 (11.9)	168 (78.9)	22 (10.2)	<0.001
Fever	274 (92.9)	167 (56.6)	181 (85.0)	106 (49.8)	0.006
Dry cough	190 (64.4)	30 (10.2)	138 (64.8)	28 (13.1)	0.995
Dyspnea	181 (61.4)	19 (6.4)	73 (34.3)	5 (2.3)	<0.001
Headache	79 (26.8)	10 (3.4)	119 (55.9)	19 (8.9)	<0.001
Asthenia	200 (67.8)	36 (12.2)	152 (71.4)	28 (13.1)	0.446
Arthromyalgia	114 (38.6)	16 (5.4)	142 (66.7)	32 (15.0)	<0.001
Diarrhea	104 (35.3)	9 (3.1)	67 (31.5)	3 (1.4)	0.424
Nausea	75 (25.4)	2 (0.7)	39 (18.3)	1 (0.5)	0.074
Nasal congestion	45 (15.3)	8 (2.7)	69 (32.4)	11 (5.2)	<0.001
Pharyngodynia	41 (13.9)	13 (4.4)	67 (31.5)	16 (7.5)	<0.001
Ocular discomfort	38 (12.9)	4 (1.4)	47 (22.1)	2 (0.9)	0.009
Syncope	25 (8.5)	3 (1.0)	17 (8.0)	1 (0.5)	0.971

TABLE 3. Demographic and clinical characteristics according to olfactory and gustatory dysfunction*

Variable	No dysfunction (n = 175)	Olfactory dysfunction		Gustatory dysfunction	
		(n = 283)	*p*[a]	(n = 321)	*p*[a]
Age (years), mean ± SD (range)	59.4 ±15.2 (24–85)	52 ± 14.4 (18–91)	<0.001	51.9 ± 14.5 (18-91)	<0.001
Gender, n (%)					
Male	121 (23.8)	138 (27.2)	<0.001	155 (30.5)	<0.001
Female	54 (10.6)	145 (28.5)		166 (32.7)	
History of smoking, n (%)					
No smoker	112 (22.0)	195 (38.4)	0.019	223 (43.9)	0.033
Current smoker [average py]	6 (1.2) [16.8 py]	23 (4.5) [11.4 py]		23 (4.5) [12.1 py]	
Former smoker [average py]	57 (11.2) [26.2 py]	65 (12.8) [18.8 py]		75 (14.8) [18.4 py]	
Comorbidities, n (%)					
None	52 (10.2)	134 (26.4)	<0.001	148 (29.1)	0.001
1–2	99 (19.5)	113 (22.2)		136 (26.8)	
>2	24 (4.7)	36 (7.1)		37 (7.3)	
Clinical management					
Hospitalized	135 (26.6)	130 (25.6)	<0.001	153(30.1)	<0.001
Home-quarantined	40 (7.9)	153 (30.1)		168 (33.1)	

*Statistical tests were used as appropriate (*t* test, chi-square test).
[a]Olfactory dysfunction vs no dysfunction, and gustatory dysfunction vs no dysfunction, respectively.
py = pack-year; SD = standard deviation.

TABLE 4. Clinical characteristics of olfactory and gustatory dysfunction

Variable	Olfactory dysfunction (n = 283)	Gustatory dysfunction (n = 321)
Degree of dysfunction		
Partial	90 (31.8)	118 (36.8)
Total	182 (64.3)	193 (60.1)
Unable to assess the degree of dysfunction	11 (3.9)	10 (3.1)
Onset (days), mean ± SD (range)		
When 1st symptom: time to the 2nd symptom[a]	4.9 ± 4.3 (1–15)	4.9 ± 4.3 (1–15)
When not 1st symptom: time after the 1st symptom[b]	4.3 ± 2.6 (1–19)	4.3 ± 2.7 (1–19)
Cases with complete resolution of the dysfunction	3.3 ± 2.7 (0–10)	3.3 ± 2.8 (0–15)
Cases with ongoing dysfunction	3.9 ± 3.2 (0–19)	3.8 ± 3.3 (0–19)
Duration of symptoms (days), mean ± SD (range)		
Cases with complete resolution of the dysfunction	9.4 ± 5.1 (2–40)	9.2 ± 5.4 (2–30)
Cases with ongoing dysfunction	12.7 ± 7.0 (1–40)	12.4 ± 6.8 (1–36)
Recovery of symptoms, n (%)[c]		
Within 14 days	118 (80.3)	143 (80.3)
After 14 days	29 (19.7)	35 (19.7)

[a]Patients affected by olfactory and gustatory dysfunction reported these complaints as single first symptom of the infection with SARS-CoV-2 in 26 cases (5.1%), with a median anticipation of 3 days compared to other symptoms. Isolated dysosmia or isolated dysgeusia have not been observed as first symptoms of presentation.
[b]Patients affected by olfactory and gustatory dysfunction reported these complains as delayed symptom of presentation of the infection with SARS-CoV-2 in 231 (81.6%) and 264 (82.2%) cases, respectively.
[c]Only patients who reported complete resolution of olfactory (147) and gustatory (178) dysfunction were considered.
SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; SD = standard deviation.

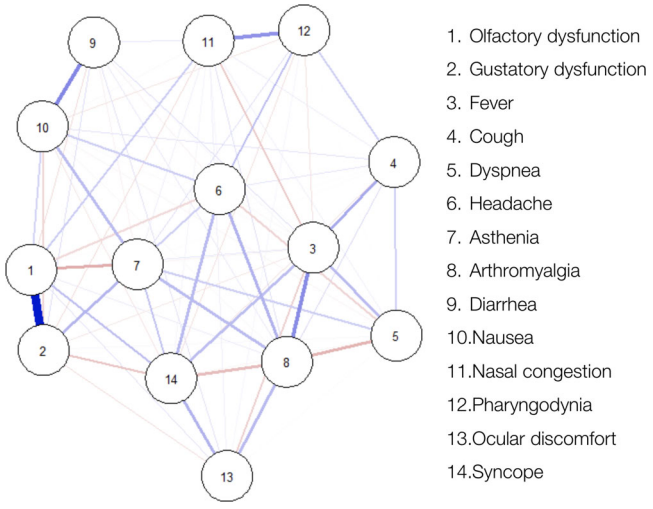

FIGURE 1. Network analysis. Blue and red lines indicate positive and negative interconnections, respectively. Thicker lines indicate stronger interconnections.

to 86% and 71% to 89%, respectively.[5,6] The sensitivity (ie, prevalence) of OD and GD should be weighed against those reported for RT-PCR (78%), CT (67%), and a combination of both (92%).[12] Nonetheless, the sensitivity of RT-PCR is extremely variable, with significant differences according to the specimen analyzed (32% in pharyngeal swabs, 63% in nasal swabs, and 93% in bronchoalveolar lavage fluid).[13] Moreover, even if the sensitivity of CT can reach values of 97% in hospitalized patients with full-blown disease, this value dramatically decreased in mildly symptomatic patients (61%).[14-16] Finally, both RT-PCR and CT may be largely impractical in an epidemic area, as they would require repetitive large-scale evaluations, thus posing evident logistic and cost-related issues. In this setting, OD and GD assessment in the general population could be a simple, cost-effective, and reliable screening tool.

Of note, we showed that the sensitivity is strictly related with the specific population analyzed (ie, hospitalized vs home-quarantined subjects). This difference is also consistent with the distinct case distribution between the 2 groups, with a higher rate of younger and otherwise healthy subjects, females, and nonsmokers being under quarantine. Moreover, the impairment associated with a severe clinical condition and a decrease in oral intake may have reduced the perception of OD and GD in the inpatient setting. In fact, hospitalized patients showed a significantly higher rate of dyspnea and a lower rate of flu-like symptoms (ie, headache, arthromyalgia, nasal congestion, pharyngodynia, and ocular discomfort).

This finding further reinforces the possible utility of OD and GD in population monitoring. In fact, the

reliability of OD and GD as biomarker of COVID-19 was higher in younger and mildly symptomatic subjects, which represents the fraction of population at a higher risk to be underdiagnosed and become active carriers of disease. In particular, this improvement in diagnosis could be particularly useful during the loosening of lockdown policy, when early detection of positive cases in workers is essential to prevent new outbreaks.

All cases with OD and GD reported an acute onset and a significant degree of dysfunction, without solid connection with other symptoms suggestive of upper airway infection (ie, pharyngodynia and nasal congestion). OD and GD were strongly correlated and clustered separately from other symptoms. These characteristics are indicative of acute sensorineural OD and GD, which is particularly uncommon in the general population.

A growing body of evidence shows that neurotropism is a common feature of coronaviruses.[17,18] Notably, SARS-CoV-1 has been found to enter the brain via the olfactory bulb and showed diffuse neuronal death in mice transgenic for human angiotensin-converting enzyme 2 (ACE2).[19] This is an important clue suggesting a similar mechanism in SARS-CoV-2, although direct proof of neuroinvasion is still not available.[20,21] Analogous damage to the olfactory epithelium and extension to the olfactory bulb has also been described in coronavirus-related sensorineural postviral olfactory dysfunction (PVOD).[22] However, differently from PVOD, in the present cohort patients were younger and experienced OD early in the course of the disease, often reporting a sudden onset and gradual, quick recovery. The identification of selective GD without OD in 10% of cases is a rarely reported occurrence in other diseases of the upper respiratory tract.[23] This phenomenon may be explained by SARS-CoV-2 infection at the level of epithelial cells of the tongue, in which the expression of ACE2 is highly enriched, similarly to what happens in the olfactory epithelium.[24,25]

Although various degrees of chronic OD and GD have a non-negligible prevalence in the general population,[26,27] impairment often occurs gradually and the patient frequently does not report significant changes in perceptual acuity until the dysfunction becomes severe.[28,29] Conversely, acute OD, often associated with hypogeusia or ageusia, is immediately recognized and can be associated with a variety of pathologic conditions, in particular acute upper respiratory infection, head trauma, toxins, and drugs.[26] In these cases, acute damage to the olfactory epithelium, olfactory fila, and gustatory epithelium can usually be identified by adequate anamnesis (ie, recent head trauma, exposure to toxic inhalants, and new medications). Furthermore, upper respiratory infection leading to olfactory and gustatory alterations is invariably associated with rhinorrhea and nasal congestion. Conversely, OD and/or GD in SARS-CoV-2 infection are weakly connected with nasal congestion and therefore suggestive of predominant sensorineural chemosensory dysfunction. Further evidence of its neurogenic nature is the high prevalence of GD without other complaints at the level of the oral cavity and, in some cases, in the absence of olfactory alterations. In this view, OD and GD of sudden onset should be safely considered as highly suggestive of COVID-19 in endemic areas and call for particular attention. Moreover, subjects with nonspecific symptoms should be carefully interrogated to identify relatives or close contacts presenting OD and/or GD to further upgrade their risk-profile according to this information. This is of paramount importance in a context of widespread domiciliary confinement imposed by government policies.

The following strengths and limitations should be highlighted. This report clearly shows the different distribution of OD and GD according to distinct populations. All patients were recruited from a specific geographic area and directly interviewed by the authors to minimize the risk of selection and reporting biases. On the other side, current policy on the execution of nasal/pharyngeal swab in our region may have introduced a selection bias, because positive asymptomatic or mildly symptomatic subjects could be largely underrepresented. The impossibility to interview patients in critical conditions prevented us from defining the prevalence of OD and GD in this group with unfavorable outcome. Recall bias should be also considered, although it is likely marginal in view of the short time-span between the interview and symptoms onset, and the precision of patient responses. Possible misclassification due to information bias should also be taken into account even if minimized by the structure of the interviews and the characteristics of the onset of the symptoms. Finally, objective tests or comprehensive questionnaires focusing on evaluation of smell and taste were not employed in view of the critical healthcare situation.

Conclusion

A radical increase in the identification and isolation of currently undocumented infections is crucial to fully control SARS-CoV-2 diffusion.[3] However, maintaining surveillance during a pandemic is particularly challenging due to shortages in testing materials and facilities. Highly suggestive symptoms such as acute olfactory and gustatory dysfunctions may facilitate the identification of infected individuals. However, the prevalence of these symptoms should be contextualized in view of their different prevalence in different patient populations.

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References

1. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. *N Engl J Med*. 2020;382:1177-1179.
2. Lipsitch M, Cohen T, Cooper B, et al. Transmission dynamics and control of severe acute respiratory syndrome. *Science*. 2003;300:1966-1970.
3. Li R, Pei S, Chen B, et al. Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV2). *Science*. 2020;368:489-493.
4. Giacomelli A, Pezzati L, Conti F, et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. *Clin Infect Dis*. (in press). Epub March 26, 2020. https://doi.org/10.1093/cid/ciaa330. Accessed June 7, 2020.
5. Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol*. (in press). Epub April 6, 2020. https://doi.org/10.1007/s00405-020-05965-1. Accessed June 7, 2020.
6. Yan CH, Faraji F, Prajapati DP, Boone CE, DeConde AS. Association of chemosensory dysfunction and COVID-19 in patients presenting with influenza-like symptoms. *Int Forum Allergy Rhinol*. (in press). Epub April 12, 2020. https://doi.org/10.1002/alr.22579. Accessed June 7, 2020.
7. Moein ST, Hashemian SMR, Mansourafshar B, Khorram-Tousi A, Tabarsi P, Doty RL. Smell dysfunction: a biomarker for COVID-19. *Int Forum Allergy Rhinol*. (in press). Epub April 17, 2020. https://doi.org/10.1002/alr.22587. Accessed June 7, 2020.
8. Yan CH, Faraji F, Prajapati DP, Ostrander BT, DeConde AS. Self-reported olfactory loss associates with outpatient clinical course in COVID-19. *Int Forum Allergy Rhinol*. (in press). Epub April 24, 2020. https://doi.org/10.1002/alr.22592. Accessed June 7, 2020.
9. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61:344-349.
10. Borghesi A, Maroldi R. COVID-19 outbreak in Italy: experimental chest X-ray scoring system for quantifying and monitoring disease progression. *Radiol Med*. 2020;125:509-513.
11. (World Health Organization (WHO). Coronavirus disease (COVID-19) technical guidance: Laboratory testing for 2019-nCoV in humans. Geneva, Switzerland: WHO; 2020. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/laboratory-guidance. Accessed June 7, 2020.
12. Jiang G, Ren X, Liu Y, et al. Application and optimization of RT-PCR in diagnosis of SARS-CoV-2 infection. *medRxiv*. 2020.02.25.20027755. https://doi.org/10.1101/2020.02.25.20027755. Accessed June 7, 2020.
13. Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA*. 2020;323:1843-1844.
14. Ai T, Yang Z, Hou H, et al. Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. *Radiology*. (in press). Epub February 26, 2020. https://doi.org/10.1148/radiol.2020200642. Accessed June 7, 2020.
15. Inui S, Fujikawa A, Jitsu M, et al. Chest CT findings in cases from the cruise ship "Diamond Princess" with coronavirus disease 2019 (COVID-19). *Radiol Cardiothorac Imaging*. 2020;2:e200110.
16. Hope MD, Raptis CA, Shah A, Hammer MM, Henry TS; six signatories. A role for CT in COVID-19? What data really tell us so far. *Lancet*. 2020;395:1189-1190. https://doi.org/10.1016/S0140-6736(20)30728-5. Accessed June 7, 2020.
17. Dube M, Le Coupanec A, Wong AHM, Rini JM, Desforges M, Talbot PJ. Axonal transport enables neuron-to-neuron propagation of human coronavirus OC43. *J Virol*. 2018;92;e00404-18.
18. Hwang CS. Olfactory neuropathy in severe acute respiratory syndrome: report of a case. *Acta Neurol Taiwan*. 2006;15:26-28.
19. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *J Virol*. 2008;82:7264-7275.
20. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol*. 2020;92:552-555. https://doi.org/10.1002/jmv.25728. Accessed June 7, 2020.
21. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. *ACS Chem Neurosci*. 2020;11:995-998.
22. Suzuki M, Saito K, Min WP, et al. Identification of viruses in patients with postviral olfactory dysfunction. *Laryngoscope*. 2007;117:272-277.
23. Pribitkin E, Rosenthal MD, Cowart BJ. Prevalence and causes of severe taste loss in a chemosensory clinic population. *Ann Otol Rhinol Laryngol*. 2003;112:971-978.
24. Xu H, Zhong L, Deng J, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int J Oral Sci*. 2020;12:8. https://doi.org/10.1038/s41368-020-0074-x. Accessed June 7, 2020.
25. Hamming I, Timens W, Bulthuis M, Lely A, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol*. 2004;203:631-637.
26. Hummel T, Whitcroft KL, Andrews P, et al. Position paper on olfactory dysfunction. *Rhinol Suppl*. 2017;54:1-30. https://doi.org/10.4193/rhino16.248. Accessed June 7, 2020.
27. Rawal S, Hoffman HJ, Bainbridge KE, Huedo-Medina TB, Duffy VB. Prevalence and risk factors of self-reported smell and taste alterations: results from the 2011-2012 US National Health and Nutrition Examination Survey (NHANES). *Chem Senses*. 2016;41:69-76.
28. Deems DA, Doty RL, Settle RG, et al. Smell and taste disorders, a study of 750 patients from the University of Pennsylvania Smell and Taste Center. *Arch Otolaryngol Head Neck Surg*. 1991;117:519-528.
29. Dalton P. Olfaction and anosmia in rhinosinusitis. *Curr Allergy Asthma Rep*. 2004;4:230-236.