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LAMPIRAN 1 : Jurnal Studi Inklusi 1

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Short communication

Features of anosmia in COVID-19

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ABSTRACT

Background. – Medical publications about anosmia with COVID-19 are scarce. We aimed to describe the prevalence and features of anosmia in COVID-19 patients.
Methods. – We retrospectively included COVID-19 patients with anosmia between March 1st and March 17th, 2020. We used SARS-CoV-2 real time PCR in respiratory samples to confirm the cases.
Results. – Fifty-four of 114 patients (47%) with confirmed COVID-19 reported anosmia. Mean age of the 54 patients was 47 (± 16) years; 67% were females and 37% were hospitalised. The median Charlson comorbidity index was 0.70 (± 1.6 [0–7]). Forty-six patients (85%) had dysgeusia and 28% presented with pneumonia. Anosmia began 4.4 (± 1.9 [1–8]) days after infection onset. The mean duration of anosmia was 8.9 (± 6.3 [1–21]) days and 98% of patients recovered within 28 days.
Conclusions. – Anosmia was present in half of our European COVID-19 patients and was often associated with dysgeusia.

1. Introduction

Clinical description from coronavirus disease 2019 (COVID-19) outbreak in China reveals that most patients (81%) present with influenza-like illness (ILI) or mild pneumonia, and 19% of cases experience severe or critical pneumonia [1]. Fever, cough, fatigue, and myalgia are usually the main symptoms. The expression of COVID-19 ILI seems non-specific; no specific symptom can lead to suspecting a case without any notion of exposure [2–7]. A major French cluster of COVID-19 began on March 1st, 2020 in the city of Mulhouse, France (less than 30 miles from our hospital). After clinical examination of the first patients, we noticed that many cases reported anosmia. The description of anosmia and other ENT symptoms is scarce with COVID-19. For instance, a recent review on COVID-19 by ENT specialists on March 26 emphasised that ENT symptoms were uncommon with COVID-19 as nasal congestion and rhinorrhea were observed in less than 5% of cases. However, they noticed that there were few reports of anosmia and dysgeusia with no real description of symptoms [8]. Recently, in April, descriptions of cases of anosmia in a multicentric cohort have been associated with COVID-19 [9–11]. We aimed to describe the prevalence and features of anosmia in COVID-19 patients.

2. Method

We conducted a retrospective observational study in the NFC (*Nord Franche-Comté*) hospital. Between March 1st and March 17th, 2020, we enrolled all adult patients (≥ 18 years) with confirmed COVID-19 who were examined at the infectious disease consultation or hospitalised in the hospital and who reported anosmia. Pregnant women, children (< 18 years), and patients with dementia (who cannot report functional symptoms) were excluded. We stopped the study follow-up on March 24th, 2020.

Diagnosis was confirmed by real-time PCR (RT-PCR) on respiratory samples, mainly nasopharyngeal swabs, sputum, bronchial aspirates, or bronchoalveolar lavage fluids. Viral RNA was extracted using the NucleoSpin® RNA Virus kit (Macherey-Nagel) according to the manufacturer's instructions, and amplified by RT-PCR protocols developed by *Charité* (E gene) [12] and the *Institut Pasteur* (RdRp gene) [13] on LightCycler 480 (*Roche*). Quantified positive controls were kindly provided by the French National Reference Centre for Respiratory Viruses, *Institut Pasteur*, Paris.

Our national guidelines recommended home follow-up for non-hospitalised patients [14]. Non-hospitalised and discharged patients were called seven days (± 7 days) after the first symptoms and every week until recovery to monitor clinical outcome.

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Data required for the study was collected from the medical files of patients: age, sex, comorbidities, features of anosmia (date of apparition since symptom onset, duration of anosmia), other symptoms, physical signs, and outcome. Usual descriptive statistics were used. Categorical variables were expressed as numbers, percentages, or mean. Continuous variables were expressed as mean with standard deviation (SD).

We aimed to describe the prevalence and characteristics of anosmia in patients with confirmed COVID-19.

3. Results

Fifty-four of 114 patients (47%) with confirmed COVID-19 reported anosmia and were included in this study. Among these 54 patients, the mean age was 47 (± 16) years and 36 (67%) were females. The median Charlson comorbidity index was 0.70 (± 1.6 [0–7]). The most frequent comorbidities were asthma (13%, $n = 7$), arterial hypertension (13%, $n = 7$), and cardiovascular disease (11%, $n = 6$). Other comorbidities were less frequent (Table 1) and no patient had chronic obstructive pulmonary disease (COPD).

Among the 54 patients, the mean duration of anosmia was 8.9 (± 6.3 [1–21]) days. Duration was ≥ 7 days for 55% (24/44) and ≥ 14 days for 20% (9/44) (Fig. 1); one patient (1/44) had not recovered at the end of the follow-up (after 28 days). Anosmia was never the first or second symptom to develop, but it was the third symptom in 38% (22/52) of cases. Anosmia developed 4.4 (± 1.9 [1–8]) days after infection onset.

As for the other ENT symptoms, anosmia was associated with dysgeusia in 85% of cases ($n = 46$). Thirty-one patients had rhinorrhea (57%) and only 16 patients (30%) had nasal obstruction. Epistaxis, tinnitus, and hearing loss were uncommon (< 15%).

As for other symptoms, seven symptoms were present in more than half of patients: fatigue (93%, $n = 50$), cough (87%, $n = 47$), headache (82%, $n = 44$), fever (74%, $n = 40$), myalgia (74%, $n = 40$), arthralgia (72%, $n = 39$), and diarrhea (52%, $n = 28$). Other symptoms were less present (Table 1).

Fifteen (28%) patients received a clinical diagnosis of pneumonia with COVID-19. Their oxygen saturation was at 94.6% [± 4.6] at admission. More than a third of our patients (37%, $n = 20$) were hospitalised, including five patients (9%) in the intensive care unit (ICU). Four patients (7%) had oxygen saturation < 90% at admission, 11 patients (20%) needed oxygen therapy during hospitalisation, and two patients (4%) died.

Table 1
Comorbidities, symptoms, and outcome of the 54 patients with anosmia.
Comorbidités, symptômes et devenir des 54 patients anosmiques.

Characteristics	Number (%)
Medical history	
Age (Y): mean (SD)	47 (± 16)
Sex	
Female	36 (67%)
Male	18 (33%)
Current smoking	6 (11%)
Comorbidities	
Arterial hypertension	7 (13%)
Cardiovascular disease[a]	6 (11%)
Diabetes	2 (4%)
Asthma	7 (13%)
COPD[b]	0 (6%)
Malignancy	2 (4%)
Immunosupression[c]	1 (4%)
Charlson comorbidity index: mean (SD)	0.70 (± 1.6, [0–7])
ENT symptoms	
Rhinorrhea	31 (57%)
Nasal obstruction	16 (30%)
Epistaxis	6 (11%)
Dysgeusia	46 (85%)
Tinnitus	6 (11%)
Hearing loss	4 (7%)
Other symptoms	
Fever measured > 38 °C	40 (74%)
Feeling of fever	12 (22%)
Highest temperature (T°C): mean (SD)	38.6 (± 0.8)
Fatigue	50 (93%)
Myalgia	40 (74%)
Arthralgia	39 (72%)
Sore throat	23 (43%)
Headaches	44 (82%)
Conjunctival hyperemia	2 (4%)
Tearing	4 (7%)
Dry eyes	2 (4%)
Blurred vision	4 (7%)
Sneezing	18 (33%)
Cough	47 (87%)
Sputum production	12 (22%)
Hemoptysis	3 (6%)
Dyspnea	21 (39%)
Respiratory rate > 22/min	10 (19%)
Sat O_2 at admission (%)	94.6 (± 4.6)
Auscultation with crackling sounds	15 (28%)
Nausea	19 (35%)
Vomiting	3 (6%)
Diarrhea	28 (52%)
Abdominal pain	15 (28%)
Outcome	
Hospitalisation	20 (37%)
Hospitalisation in the intensive care unit	5 (9%)
Oxygen therapy	11 (20%)
Death	2 (4%)

[a] Defined by: cardiac failure, cardiac arrhythmia, coronary heart disease, stroke, peripheral arterial obstructive disease, and thromboembolic disease.
[b] Chronic obstructive pulmonary disease.
[c] Defined by: transplantation, cirrhosis, long-term steroid therapy, and immunomodulator treatments.

4. Discussion

A multicentric European study published on April 6 conducted by Lechien et al. reported 357 patients with olfactory dysfunction related to COVID-19 [11]. We mostly used this publication to discuss our results, as it is the only publication with a large cohort of patients with COVID-19-related olfactory dysfunction.

The mean age of our population was 47 (± 16) years, and 67% were females. The prevalence of asthma in our study was ≥ 10% and we did not have any COPD patient, which is uncommon in patients with COVID-19. Patients with anosmia seemed to be younger with a predominance of females, they had fewer comorbidities with a lower Charlson comorbidity index (< 1), and more often presented with asthma in comparison with the population usually described with COVID-19; the same population characteristics were described by Lechien et al.

Until recently, ENT symptoms had not been reported with COVID-19, except for nasal congestion and rhinorrhea [2–8]. However, 54 (47%) of our 114 COVID-19 patients reported anosmia. Lechien et al. reported anosmia in 86% ($n = 357/417$) of their patients. This higher frequency may be explained by their population profiles, which were ambulatory cases that consulted at ENT consultations (patients with a mean age of 37 [± 11.4] years without cardiovascular comorbidities) and for whom it is probably easier to relate functional symptoms than patients with oxygen therapy or critical patients. Anosmia was therefore a frequent symptom in COVID-19 patients in our French study and in this European study. However, few descriptions of ENT symptoms are available, especially in Asian studies. These differences between Asia and Europe should be discussed. We made several assumptions. First, the theoretical possibility of a mutation of SARS-CoV-2 viral genome associated with a clinical impact, but not yet

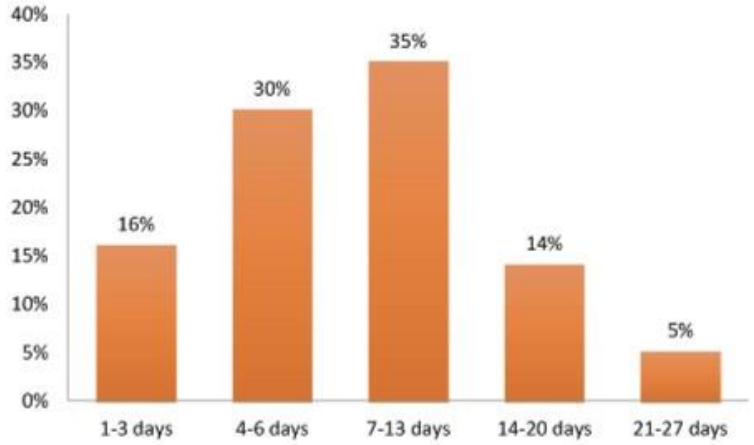

Fig. 1. Recovery time for patients with anosmia ($n = 43$ patients, 10 patients did not remember duration until recovery and one patient did not recover after 28 days).
Durée de l'anosmie (n=43, 10 patients ne se rappelaient pas de la durée et 1 patient était toujours anosmique à J28).

described. On the other hand, it is difficult to precisely report ENT symptoms of critical patients. These symptoms may seem of less importance when considering the potential severity of the disease [15]. Finally, Lechien et al. discussed the affinity of SARS-CoV-2 for tissues and individual possible genetic features. Their main argument was that the angiotensin-converting enzyme 2 (as receptor of SARS-CoV-2) can be specific to an ethnic group.

Anosmia was associated with dysgeusia in 85% of cases and in more than half of cases with rhinorrhea (57%). However, 70% of our patients with anosmia did not present with nasal obstruction. This leads to suspecting another pathogenesis for anosmia than mechanical nasal obstruction. In addition, anosmia during viral rhinitis with nasal obstruction usually resolves within three days [16], while we observed a mean duration of anosmia of nine days. The concept of anosmia after viral infection is known as post-infectious/post-viral olfactory loss (POL). Different kind of viruses can induce POL, including coronaviruses such as HCoV-229E [17]. However, medical literature data indicates that the duration of POL can be long: a study of 63 patients with POL reported that after one year 80% of patients had subjective recovery [18]. In our study, only one patient did not recover at the end of the study follow-up (after a follow-up of 28 days); 80% of our patients recovered within 14 days. Compared with POL, the outcome of COVID-19-related acute anosmia most frequently seems favourable in the short term.

Our patients had the same other symptoms (other than ENT symptoms) as those reported in other studies [2–7]. However, just like Lechien et al., we observed that diarrhea was reported in more than 50% of patients. Except for one study (occurrence of 33%), the occurrence of diarrhea is < 20% in the medical literature [19]. The frequency of diarrhea seems to be high in patients with anosmia.

One of our study limitations was the limited number of patients. However, our study is, to our knowledge, the main monocentric cohort of confirmed COVID-19 patients with anosmia in France and in the medical literature. Our results are similar to those published by the recent multicentric European study performed by Lechien et al.

5. Conclusion

COVID-19-related anosmia is a new description in the medical literature. Half of the patients with COVID-19 present with anosmia. Anosmia is associated with dysgeusia in more than 80% of cases. The outcome seems favourable in less than 28 days. This notion needs to be communicated to the medical community.

Contribution of authors

SZ and JNKO collected the epidemiological and clinical data. TK and SZ drafted the article. LT, PYR, QL, and VG reviewed the final version of the article.

Disclosure of interest

The authors declare that they have no competing interest.

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LAMPIRAN 2 : Jurnal Studi Inklusi 2

ORIGINAL ARTICLE

Smell dysfunction: a biomarker for COVID-19

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Background: **Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), is responsible for the largest pandemic since the 1918 influenza A virus subtype H1N1 influenza outbreak. The symptoms presently recognized by the World Health Organization are cough, fever, tiredness, and difficulty breathing. Patient-reported smell and taste loss has been associated with COVID-19 infection, yet no empirical olfactory testing on a cohort of COVID-19 patients has been performed.**

Methods: **The University of Pennsylvania Smell Identification Test (UPSIT), a well-validated 40-odorant test, was administered to 60 confirmed COVID-19 inpatients and 60 age- and sex-matched controls to assess the magnitude and frequency of their olfactory dysfunction. A mixed effects analysis of variance determined whether meaningful differences in test scores existed between the 2 groups and if the test scores were differentially influenced by sex.**

Results: **Fifty-nine (98%) of the 60 patients exhibited some smell dysfunction (mean [95% CI] UPSIT score: 20.98 [19.47, 22.48]; controls: 34.10 [33.31, 34.88]; $p < 0.0001$). Thirty-five of the 60 patients (58%) were either anosmic (15/60; 25%) or severely microsmic (20/60; 33%); 16 exhibited moderate microsmia (16/60; 27%), 8 mild microsmia (8/60; 13%), and 1 normosmia (1/60; 2%). Deficits were evident for all 40 UPSIT odorants. No meaningful relationships between the test scores and sex, disease severity, or comorbidities were found.**

Conclusion: **Quantitative smell testing demonstrates that decreased smell function, but not always anosmia, is a major marker for SARS-CoV-2 infection and suggests the possibility that smell testing may help, in some cases, to identify COVID-19 patients in need of early treatment or quarantine.** © 2020 ARS-AAOA, LLC.

Key Words:
chronic rhinosinusitis; olfactory disorders; olfaction; olfactory test; UPSIT; COVID-19; biomarker

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Recently there have been numerous reports in the media that anosmia occurs in persons who have contracted coronavirus disease 2019 (COVID-19) by exposure to the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) virus. These include 1 published single case report,[1] and self-report surveys from Germany,[2] Great Britain,[3] Iran,[4] Italy,[5] and the United States,[6] with smell loss reports ranging from 34% to 68% of COVID-19–positive patients. Otorhinolaryngology authorities have warned that loss of smell and taste, in combination with other symptoms, appears to be a strong predictor of COVID-19 infection.[7,8]

To date, validated quantitative olfactory testing has not been performed in a cohort of COVID-19 patients to

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verify or determine the true magnitude of their deficits and whether less-than-total loss occurs in some patients. Moreover, the proportion of COVID-19 patients exhibiting true olfactory disturbances is unknown. Most studies suggest that, in general, a significant number of persons with smell loss are unaware of their deficit until formal testing[9] and that self-reports of both smell and taste abilities correlate poorly with the results of quantitative smell and taste tests.[10,11]

In this case-control study, we administered the Persian version of the 40-item University of Pennsylvania Smell Identification Test (UPSIT)[12] to 60 confirmed COVID-19 patients and 60 age- and sex-matched controls to assess the presence, magnitude, and frequency of their olfactory dysfunction. We determined whether the smell loss was related to the sex of the subjects and inquired, for those patients who were aware of their dysfunction before testing, when they first noticed their chemosensory disorder.

Patients and methods

Subjects

The age, sex, comorbidities, smoking status, and complaints of chemosensory dysfunction of the 120 study participants are presented in Table 1. The 60 SARS-COV-2–positive subjects had been admitted with the symptoms of COVID-19 to the Masih Daneshvari Hospital, Tehran, Iran, between March 21, 2020, and March 23, 2020, or March 31, 2020, and April 5, 2020. At the time of the olfactory testing, all were inpatients in the recovery period of the disease and were ready to be discharged within 4 days. The study was explained in detail to 68 such patents, of which 8 declined to participate (ie, the participation rate was 88%).

The control subjects were from a database of 141 subjects collected in Iran for an earlier study. They were tested in the olfactory laboratory of the Institute for Research in Fundamental Sciences, Tehran, Iran, and comprised a convenience sample obtained from e-mail lists, flyers, and word of mouth. None had influenza or common cold symptoms at the time of testing. The recruitment period for this database (August 8, 2019, to February 13, 2020) preceded the first reported confirmed cases of COVID-19 in Iran (February 19, 2020). A control subject was individually matched as closely as possible to each COVID-19 patient. Exact age matches were possible for 34 subjects, 1-year differences for 22 subjects, and 2-year differences for 4 subjects. In cases where >1 match was possible, the first match in the database sequence was used.

Informed written consent was obtained from each patient and control, and the study protocol was approved by the local ethics committee and the Iranian Ministry of Health (license number IR.SBMU.NRITLD.REC.1399.013). All testing was performed with the highest regard for examiner safety with appropriate personal protective equipment.

TABLE 1. Patient and control subject demographics*

Parameter	COVID-19 patients	Controls	*p* (Fisher exact probability test)
Sample size, n	60	60	
Age (years), mean ± SD	46.55 ± 12.17	46.55 ± 12.07	
Gender (male/female), n	40/20	40/20	
Smoker (current/never), n	2/58	11/49	**0.016**
Taste/smell complaints, n	21	0	**0.001**
Comorbidities, n			
Asthma	3	0	0.244
Atherosclerosis	0	2	0.496
Autoimmune disease	4[a]	0	0.119
Carcinoma	2[b]	0	0.496
Congenital melanocytic nevi	1	0	1.000
Diabetes	8[c]	0	**0.007**
Hemophilia	0	1	1.000
Hepatic failure	0	1	1.000
Hyperlipidemia	1	1	1.000
Hypertension	6[c]	5	1.000
Hypothyroidism	4[c]	2	0.679
Migraine	0	1	1.000
Osteoporosis	0	1	1.000
Sinusitis	2	0	0.496

*Significant *p* differences indicated in bold.
[a]Autoimmune disease included Behcet's disease in combination with Crohn's disease (n = 1), multiple sclerosis (n = 2), and rheumatoid arthritis (n = 1).
[b]Prostate and cervical cancers.
[c]Although, in rare cases, changes in dosage and medications may have occurred during the course of inpatient treatments, most patients remained on their preadmission medications.
COVID-19 = coronavirus disease 2019; SD = standard deviation.

Diagnosis and clinical severity classification of COVID-19 patients

COVID-19 diagnosis was based on the COVID-19 detection protocol of Masih Daneshvari Hospital. All of the patients underwent 16-slice chest computed tomography (CT) imaging (Scope Power Siemens CT Scan, Munich, Germany) and had positive chest CT findings.[13] Subsequently, the diagnosis of COVID-19 disease was confirmed by quantitative detection of SARS-CoV-2 RNA using the real-time reverse-transcription polymerase chain reaction (rRT-PCR) in respiratory specimens.[14] The RT-PCR assays were performed using Sansure Biotech's 2019-nCoV 30-Minute Nucleic Acid Reagent Kits (Sansure Biotech, Inc., Development Zone, Changsha, China). The respiratory specimens were

collected from the patients' nasopharyngeal wash/aspirate or nasal aspirate.

COVID-19 clinical severity was classified as mild, moderate, or severe according to the Massachusetts General Hospital COVID-19 treatment guidance algorithm.[15] Mild clinical COVID-19 presentation was defined as having oxygen saturation (SpO_2) >90% along with or without risk factors. Moderate clinical COVID-19 presentation was considered for patients who had at least 1 epidemiological risk factor along with a risk factor in vital signs or laboratory findings at the admission point of time. Patients in the intensive care unit (ICU) or with progressive disease were classified as having severe clinical presentation of COVID-19. Epidemiological risk factors included age >55 years or preexisting pulmonary disease, chronic kidney disease, diabetes with glycated hemoglobin (A1c) >7.6%, history of hypertension or cardiovascular disease or transplant, or immunosuppression or human immunodeficiency virus (HIV). Risk factors of vital signs comprised respiratory rate >24 breaths/minute, heart rate >125 beats/minute, and SpO_2 <90% on ambient air. In laboratory findings, fibrin degradation product D-dimer >1000 ng/mL, creatine phosphokinase (CPK) more than twice the upper limit of normal, C-reactive protein (CRP) >100 mg/L, lactate dehydrogenase (LDH) >245 U/L, elevated troponin, admission absolute lymphocyte count <0.8, and ferritin >300 μg/L. For COVID-19 patients with mild disease with SpO_2 >90%, supportive care was provided and hydroxychloroquine administration was started (200 mg twice per day [BID] × 2 doses, then 100 mg BID for 5 days). For the patients with moderate to severe COVID-19 presentations, lopinavir/ritonavir 200/50 mg BID for up to 10 days) was prescribed. In patients with progressive COVID-19 disease admitted to the ICU, intravenous immunoglobulin (IVIG) at standard dose of 0.5 g/kg/day daily for 5 days was administered.[16]

Olfactory testing

A modified and validated Persian version of the UPSIT was administered in this study (Sensonics International, Haddon Heights, NJ). The UPSIT is a well-validated and reliable (test-retest $r = 0.94$) test that employs microencapsulated "scratch and sniff" odorants.[11,12,17,18] It provides an index of absolute dysfunction (ie, anosmia, severe microsmia, moderate microsmia, mild microsmia, normosmia, malingering), as well as relative dysfunction based upon age- and gender-adjusted normative percentile ranks. The total number of odorant stimuli out of 40 that is correctly identified serves as the test measure. Scores on this test correlate well with other types of olfactory tests, including threshold tests.[19] Although the UPSIT is designed to be self-administered, to be certain that the COVID-19 patients correctly performed the test during the limited clinical time window, the testing was assisted by a trained examiner.

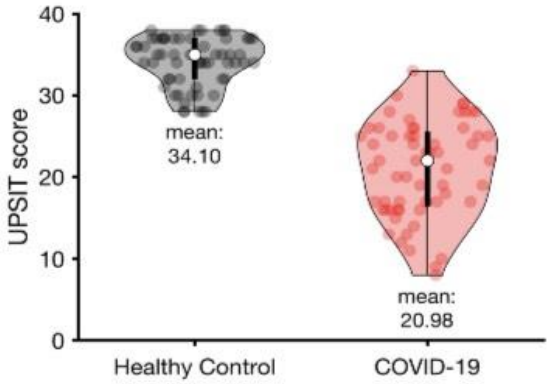

FIGURE 1. UPSIT scores of the COVID-19 patients compared to those of healthy controls. The distribution of the participants' scores in each group is depicted in violin plot. The white circles indicate the median of the score for each group. COVID-19 = coronavirus disease 2019; UPSIT = University of Pennsylvania Smell Identification Test.

Statistical analyses

Statistical analyses were performed using either SYSTAT 13 (Systat Software, Inc., San Jose, CA)[20] or MATLAB 2019b (The MathWorks, Inc., Natick, MA). A subject group by gender mixed factor analysis of variance (ANOVA) was used to determine whether the UPSIT scores differed significantly between the patient and control groups and whether gender influenced the test scores. Standard ANOVAs were used to compare other means. Differences in frequencies were assessed using the Fisher's exact probability test.

Results

The COVID-19 patients' non-mutually exclusive presenting symptoms were fever (n = 46, 77%), cough (n = 35, 58%), shortness of breath (n = 31, 52%), headache (n = 22, 37%), myalgia (n = 5, 8%), sweating (n = 2, 3%), shivering (n = 2, 3%), anorexia (n = 2, 3%), stomachache (n = 1, 2%), and tinnitus (n = 1, 2%). The mean (95% CI) time between the onset of symptoms and the olfactory testsing was 12.76 (11.47, 14.06) days.

The UPSIT testing revealed that, relative to controls and published normative data, the COVID-19 patients exhibited marked olfactory dysfunction. Thus, as illustrated in Figure 1, the mean (95% confidence interval [CI]) UPSIT score for the COVID-19 patients was 20.98 (19.47, 22.48), reflecting severe microsmia,[21] whereas the mean UPSIT score (95% CI) for the age- and sex-matched controls fell within the normal range (34.10 [33.31, 34.88]; ANOVA group main effect $F[1,58] = 232.99$, $p < 0.0001$, $\eta^2 = 0.80$). The COVID-19 deficit was not specific to any 1 UPSIT odorant, being evident for all 40 stimuli (Fig. 2).

Importantly, all but 1 of the 60 patients with COVID-19 had some degree of measured olfactory dysfunction (98%). Thirty-five of the 60 patients (58%) were either anosmic

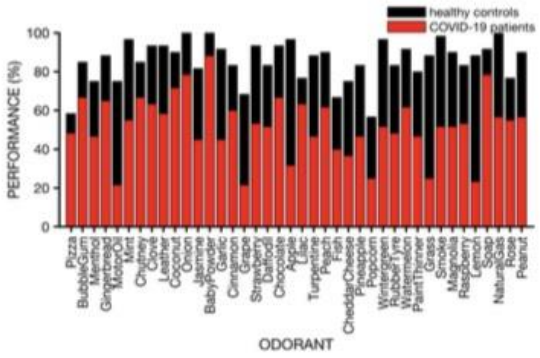

FIGURE 2. Performance on individual UPSIT odorants for the COVID-19 patients and matched healthy controls. Note that dysfunction was evident for all 40 UPSIT odorants. Performance for each group is calculated as the percent of individuals having correctly identified the odorant. COVID-19 = coronavirus disease 2019; UPSIT = University of Pennsylvania Smell Identification Test.

TABLE 2. Classification of olfactory function of the UPSIT scores of COVID-19 patients and matched controls

UPSIT function category	COVID-19 patients n (%)	Controls n (%)	UPSIT score range
Normosmia	1 (2)	49 (82)	31–40
Mild microsmia	8 (13)	11 (18)	28–30
Moderate microsmia	16 (27)	0	24–27
Severe microsmia	20 (33)	0	17–23
Anosmia	15 (25)	0	6–16
Probable malingering	0	0	0–5

COVID-19 = coronavirus disease 2019; UPSIT = University of Pennsylvania Smell Identification Test.

(15/60; 25%) or severely microsmic (20/60; 33%); 16/60 (27%) exhibited moderate microsmia, 8/60 (13%) mild microsmia, and 1/60 (2%) normosmia according to Persian-adjusted UPSIT norms (Table 2).[21] This contrasts markedly from the controls, of which 49 of 60 (82%) were normal with the remaining 11 of 60 (18%) having only mild borderline dysfunction. Relative to the normal controls, the 11 controls with mild borderline dysfunction tended to be disproportionately men (10/11 [91%] vs 30/49 [61%]; $p = 0.08$) of older age (respective mean ages [95% CIs] = 51.18 [42.63, 59.73] and 45.51 [42.11, 48.90]; $p = 0.18$). Even though there was a tendency for women, overall, to outperform men on the UPSIT (respective mean [95% CI] UPSIT scores: 22.55 [20.13, 24.97] and 20.20 [18.27, 22.13]; F [1,58] = 3.82, $p = 0.055$, $\eta^2 = 0.06$), this was unrelated to COVID-19 (sex by group interaction F [1,58] = 0.396, $p = 0.53$).

Thirty-five percent (21/60) of the COVID-19 patients reported a loss in either smell or taste function, with 12% (7/60) reporting smell loss only, 7% (4/60) taste loss only,

TABLE 3. Relationship between COVID-19 clinical disease severity and mean (95% CI) scores on the UPSIT

COVID-19 disease severity	n (%)	UPSIT score mean (95%CI)
Mild	25 (42)	22.04 (20.11–24.72)
Moderate	29 (48)	19.69 (17.24–21.99)
Severe	6 (10)	22.83 (17.65–25.77)

CI = confidence interval; COVID-19 = coronavirus disease 2019; UPSIT = University of Pennsylvania Smell Identification Test.

and 17% (10/60) both taste and smell loss. There was no significant difference between UPSIT scores of patients who were aware or unaware of their chemosensory loss ($p = 0.28$). All 21 reported that the onset of the olfactory dysfunction occurred at the same time or immediately after the onset of their other COVID-19 symptoms. None reported recognizing any smell or taste deficits prior to their other COVID-19 symptoms, namely fever, cough, or shortness of breath. In the healthy control group, none of the participants reported any smell or taste problems.

As shown in Table 1, significantly fewer smokers were present in the COVID-19 group than in the control group (2/60 vs 11/60; $p = 0.016$). Eight patients with diabetes were present in the COVID-19 group, unlike the control group (8/60 vs 0/60; $p = 0.007$). However, the respective mean (95% CI) UPSIT scores for COVID-19 patients with and without diabetes did not differ (21.38 [18.18, 24.56] vs 20.92 [19.32, 22.62], respectively; F [2,57] = 1.43, $p = 0.24$, $\eta^2 = 0.05$). No association of UPSIT scores with disease severity, as per the Massachusetts General Hospital COVID-19 treatment guidance algorithm, was apparent (Table 3; F [2,57] = 1.45, $p = 0.24$, $\eta^2 = 0.05$).

Discussion

This study quantitatively evaluated olfaction in a sizable cohort of patients diagnosed with the SARS-CoV-2 virus infection. By employing a well-validated 40-item smell test, COVID-19 patients were able to be classified into distinct categories of olfactory dysfunction, with 35 of 60 (58%) exhibiting either anosmia or severe microsmia. In the present study, only 35% of the patients were aware of their olfactory deficit before testing, a percentage near to that of 34% reported in an interview with COVID-19 inpatients in Italy,[5] but lower than those reported in 2 online surveys (59%[3] and 68%[6]). This difference between self-report rate and quantified smell assessment conceivably reflects a disproportionate sampling of hospital admitted cases and/or the well-documented underestimation of self-reported smell and taste dysfunction present for the general population[9,10] and for such diseases as Alzheimer's disease (AD)[11] and Parkinson's disease (PD).[22,23] In general, smell loss is most noticeable when marked loss, such as anosmia, is present.[11,22] It should be pointed out that

the present study's sample resembles the demographic and clinical characteristics of COVID-19 patients reported in a compilation of 43 studies involving 3600 patients,[24] implying it is likely representative of COVID-19 patients in general.

The basis for the smell loss due to SARS-CoV-2 is not entirely clear, although it is well established that viruses and other xenobiotics can damage the olfactory neuroepithelium. Indeed, acute viral upper respiratory viral infections that damage this epithelium are the major cause of chronic olfactory dysfunction and numerous viruses are known to enter the brain through cellular and pericellular transport via this epithelium.[25] In North America, the peak period of non-influenza–related smell loss, including that possibly due to coronaviruses, occurs during the months of April, May, and June, whereas influenza-related smell loss peaks in December, January, and February.[26] Currently, the prevalence of COVID-19 in North America seems to follow a similar function to that observed for olfactory deficits due to other viruses, including other coronaviruses. What seems unique, however, is that nearly everyone who contacts COVID-19 appears to exhibit measurable loss of smell seemingly independent of severe nasal congestion or inflammation.

Although SARS-CoV-2 has the ability to enter epithelial cells by directly binding to the angiotensin converting enzyme 2 (ACE2) protein on the cell surface,[27] olfactory receptor cells do not express ACE2, as well as another gene involved in SARS-CoV-2 entry (TMPRSS2), unlike epithelial sustentacular and stem cells.[28] Thus, damage to the olfactory receptors may be mediated indirectly through SARS-CoV-2 uptake into other cells critical for sustaining the olfactory receptor cell population. For example, olfactory ensheathing glial cells that surround the olfactory receptor cell axons and form the olfactory fila are 1 candidate by which ACE2-independent virus transfer can occur into olfactory receptor neurons by way of exosomes. A possible scenario suggests that at this point olfactory receptor neurons may initiate a rapid immune response in the host with the manifestation of olfactory dysfunction.[29] That being said, the olfactory neuroepithelium has considerable propensity for regeneration if the stem cell layer is not markedly damaged[30-32] – regeneration that is likely related to spontaneous improvement in olfactory function over time.[33]

It is of interest that significantly fewer smokers were found in our COVID-19 cohort than in the control cohort. Our findings correspond with studies that report current smokers as rare as 1.4% and 1.3% in Chinese[34] and U.S.[35] COVID-19 patient populations, respectively. A recent study reported that smoking upregulated the expression of ACE-2 in the airways, potentially predisposing individuals to increased risk of coronavirus infection but, paradoxically, protecting the host against acute lung injury.[36] Interestingly, nonsmokers appear to be much more susceptible than smokers to olfactory dysfunction from industrial exposures to acrylate and methacrylate[37] and smoking appears to protect, to some degree, against the olfactory loss of PD.[38] Future research is needed to determine to what degree the reported low frequency of smokers in COVID-19 populations is impacted by selection bias (eg, more smokers may have died before reaching the hospital) and reverse causation (ie, cessation of smoking in patients with severe symptoms prior to entering the hospital, thereby being counted as nonsmokers). The latter is unlikely in our study, however, because each patient was specifically asked whether they currently smoked or had smoked in the past.

The complaint of taste loss by a small number of our COVID-19 patients most likely reflects, to a significant degree, damage to the olfactory system, rather than damage to the taste buds or taste afferents, per se. Thus, the vast majority of individuals who clinically present with complaints of taste loss actually exhibit smell dysfunction, including those with a viral etiology.[39] Taste bud–mediated sensations are largely limited to the basic taste qualities of sweet, sour, bitter, salty, and umami. With the exception of such sensations, all "tastes" are flavor sensations from olfactory receptor stimulation by volatiles entering from the nasopharynx during deglutition.[40] This tendency for many persons with smell loss to misconstrue their problem as taste loss[39] must be considered in studies relying only on self-report. Future research employing quantitative taste tests is clearly needed to definitively establish whether SARS-CoV-2 also can damage taste afferents or, in rare cases, more central taste-related brain regions.

More men than women were present in our sample, in accord with the reported demographic and clinical characteristics of COVID-19 patients.[24] However, the magnitude of olfactory dysfunction, as measured by the UPSIT, was essentially the same in both sexes. This implies that there is little or no protection from being a female in terms of the degree to which SARS-CoV-2 damages the olfactory system, in accord with some other studies of postviral olfactory deficits.[41] If this observation is confirmed with larger samples, it would appear that the olfactory dysfunction of COVID-19 differs from that of AD and PD, where women significantly outperform men.[11,22,38]

It is important to note that the COVID-19–positive patients evaluated in this study had severe enough symptoms to be admitted to the hospital. It is unknown whether less severe cases also exhibit the same degree of smell dysfunction as documented in this study, although within our hospitalized cohort no relationship was evident between the olfactory test scores and disease severity. This is similar to what is seen in the smell loss of PD, where no clear association is present between the magnitude of the classic motor signs and the amount of olfactory dysfunction.[22]

Even though the COVID-19 patients in this study were undergoing drug treatments for their disease, it is unlikely that the involved drugs were a meaningful cause of their olfactory dysfunction. Despite the fact that a significant number of medications are reported to have taste side effects,[42] alterations in smell function are relatively rare and have

not been associated with hydroxychloroquine, lopinavir-ritonavir, or IVIG. Because the same degree of smell function was evident among patients with COVID-19 taking each of these medications, it is improbable that any one medication would have produced the smell deficits observed in this study.

Although RT-PCR was by far the frontline response to the SARS-CoV-2 outbreak, the accuracy and conditions under which the results of RT-PCR were achieved must be kept in context, because a false-negative rate of at least 15% has been reported.[43-45] The present findings, along with the wealth of anecdotal data, suggest that quantitative testing of the sense of smell might serve as a rapid and inexpensive alternative diagnostic means to screen for COVID-19 in large numbers of individuals. Indeed, the sensitivity and specificity of olfactory tests for COVID-19–positive patients under the age of 65 years would seem to be quite strong, because age-related changes in smell function occur mainly after the age of 65 years.[17]

The present study has both strengths and weaknesses. Among its strengths are (1) the use of a sensitive test of olfactory function that allows for determining different degrees of olfactory function, (2) testing of well-validated COVID-19 patients whose clinical severity was well documented, and (3) the use of controls matched closely to those of the patients on the basis of age and sex who were sampled outside of the period in which COVID-19 was first identified in Iran. Its major limitation is the sampling of the study population at only 1 point in time relative to the onset of COVID-19 symptoms. Future studies are needed to establish (1) the exact time of onset of smell symptoms, (2) whether the olfactory dysfunction is transient, long-lasting, or permanent, (3) whether such symptoms are evident in those who fail to develop other COVID-19 symptoms, and (4) whether the deficits follow seasonal patterns such as those noted for other virus-related cases of smell dysfunction.[26] Information as to permanency is of considerable significance, because loss of the ability to smell significantly impacts quality of life, the flavor of foods, and beverages, and safety from spoiled food, fire, and leaking natural gas. Importantly, smell loss can be a harbinger of a number of neurological diseases, most notably AD and PD—diseases which, in some cases, have been associated with a number of viruses.[46,47] Although the reasons are poorly understood, older persons with smell loss are 3 times more likely to die over the course of an ensuring half-decade than older persons with a normal sense of smell.[48,49]

Conclusion

The present study provides a quantitative assessment of the olfactory function of a cohort of patients with COVID-19. Its findings strongly suggest that some degree of loss of smell function is present in nearly all COVID-19 patients near the end of their acute recovery period. However, anosmia, per se, was present in only about one-quarter of COVID-19 positive patients in our sample, with about one-third evidencing severe microsmia. In light of the current findings and pandemic environment, and the widespread anecdotal evidence of smell dysfunction in COVID-19, it does not seem unreasonable that testing the olfaction of persons who may be at risk or have subtle COVID-19 signs, such as low-grade fevers, may aid in identifying COVID-19 patients who are in need of early treatment or quarantine.

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LAMPIRAN 3 : Jurnal Studi Inklusi 3

ORIGINAL ARTICLE

Association of chemosensory dysfunction and COVID-19 in patients presenting with influenza-like symptoms

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Background: **Rapid spread of the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) and concern for viral transmission by ambulatory patients with minimal to no symptoms underline the importance of identifying early or subclinical symptoms of coronavirus disease 2019 (COVID-19) infection. Two such candidate symptoms include anecdotally reported loss of smell and taste. Understanding the timing and association of smell/taste loss in COVID-19 may help facilitate screening and early isolation of cases.**

Methods: **A single-institution, cross-sectional study evaluating patient-reported symptoms with a focus on smell and taste was conducted using an internet-based platform on adult subjects who underwent testing for COVID-19. Logistic regression was employed to identify symptoms associated with COVID-19 positivity.**

Results: **A total of 1480 patients with influenza-like symptoms underwent COVID-19 testing between March 3, 2020, and March 29, 2020. Our study captured 59 of 102 (58%) COVID-19-positive patients and 203 of 1378 (15%) COVID-19-negative patients. Smell and taste loss were reported in 68% (40/59) and 71% (42/59) of COVID-19-positive subjects, respectively, compared to 16% (33/203) and 17% (35/203) of COVID-19-negative patients ($p < 0.001$). Smell and taste impairment were independently and strongly associated with COVID-19 positivity (anosmia: adjusted odds ratio [aOR] 10.9; 95% CI, 5.08-23.5; ageusia: aOR 10.2; 95% CI, 4.74-22.1), whereas sore throat was associated with COVID-19 negativity (aOR 0.23; 95% CI, 0.11-0.50). Of patients who reported COVID-19-associated loss of smell, 74% (28/38) reported resolution of anosmia with clinical resolution of illness.**

Conclusion: **In ambulatory individuals with influenza-like symptoms, chemosensory dysfunction was strongly associated with COVID-19 infection and should be considered when screening symptoms. Most will recover chemosensory function within weeks, paralleling resolution of other disease-related symptoms.** © 2020 ARS-AAOA, LLC.

Key Words:
COVID-19; smell loss; taste loss; patient outcomes

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The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) continues to spread at an exponential rate with recent concerns of significant viral transmission through asymptomatic or mildly symptomatic patients.[1] Anecdotal reports suggest smell and taste loss are potential early symptom or subclinical markers of COVID-19 infection. A preliminary study from Iran showed a significant increase in new-onset anosmia since the COVID-19 outbreak.[2] An Italian report of 59 hospitalized COVID-19 patients found that 33% reported a chemosensory disorder.[3] However, it remains unclear if these findings are unique to COVID-19 infections requiring hospitalization, causally related to COVID-19 infection, or simply due to more widespread recognition of postviral anosmia. Insight into the timing and association of smell/taste loss and COVID-19 is critical because patients

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with acute anosmia may be otherwise asymptomatic carriers of infection who may unwittingly facilitate the spread of disease.

Patients and methods

Study design and population

A single institution, cross-sectional study evaluating patient-reported symptoms with a focus on smell and taste was conducted using an Internet-based platform (Qualtrics, Provo, UT) on adult subjects who underwent polymerase chain reaction (PCR)-confirmed testing for COVID-19 between March 3, 2020, and March 29, 2020. An initial email invitation to a 27-question survey was sent to 102 subjects who tested COVID-19–positive and 1378 subjects who tested COVID-19–negative, with a follow-up phone call. Sense of smell at baseline, at the time of COVID-19 testing, and at the time of survey were assessed using a subjective olfaction score. Questions were based off a continuous 10-point slide bar (0: no sense of smell, 10: normal sense of smell), with scores from 1 to 9 indicating progressively increasing severity of hyposmia. This study was approved by the Institutional Review Board of University of California San Diego (IRB# 200485).

Statistical analysis

Categorical variables were evaluated by chi-square (χ^2) test. Unadjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated by univariable logistic regression, with COVID-19 test result considered as the independent variable. Adjusted ORs (aORs) were calculated using multivariable logistic regression analysis, a priori criteria for variable inclusion in the multivariable model included: (1) maximum of 6 variables to minimize potential model overfitting; (2) magnitude of association with COVID-19 positivity of at least 2-fold (ie, OR $\geq$ 2.0 or OR $\leq$ 0.5); (3) statistically significant associations ($p < 0.05$); and (4) we prioritized "any symptoms" (eg, any symptoms reported during the entire disease period) over "presenting symptoms" (eg, initial symptoms of presentation) because we had no a priori hypothesis for the natural history of anosmia and thus believed that inputting "any symptoms" for our multivariate correlation analyses would be more sensitivity for establishing associations between anosmia/ageusia and COVID-19 status. Given the known colinear relationship between anosmia and ageusia, each variable was adjusted separately as a dependent variable. Goodness-of-fit was performed for both final multivariable models (anosmia and ageusia). All permutations of models tested showed p values >0.05, demonstrating that goodness-of-fit of both final models as evaluated by both Pearson's method (anosmia $p = 0.64$, ageusia $p = 0.44$), as well as Hosmel-Lemeshow's method (anosmia $p = 0.36$, ageusia $p = 0.11$), demonstrated that our models fit the data well. Analysis was performed using Stata 15.1 software (StataCorp, College Station, TX).

Results

A total of 59 COVID-19–positive (58% response rate) and 203 COVID-19–negative subjects completed the survey (15% response rate) between March 31, 2020, and April 3, 2020. Demographics and clinical characteristics of the 2 cohorts are summarized in Table 1. There were no differences in regard to age (grouped by decade) or rate of illness improvement between the 2 groups. Hospital admission rates were low and comparable in both groups (4/58 [7%] of COVID-19–positive patients and 14/200 [7%] COVID-19–negative patients, χ^2 test $p = 0.98$), with predominantly ambulatory cases responding to the survey. The patients who were later found to be COVID-19–negative were admitted for evaluation of fever and/or dyspnea. Sex distribution in COVID-19–positive patients was balanced, but was skewed toward females (65%) in COVID-19–negative patients.

Olfactory and gustatory impairment was reported in (40/59) 68% and (42/59) 71% of COVID-19–positive patients, respectively, compared to 16% and 17% of COVID-19–negative patients (χ^2 test $p < 0.001$). Two patients reported acute ageusia without acute anosmia due to a preexisting history of baseline chronic rhinosinusitis–associated anosmia. Self-reported symptoms associated with COVID-19 positivity in order of descending frequency included fatigue (81%), ageusia (71%), fever (70%), anosmia (68%), myalgia or arthralgia (63%), diarrhea (48%), and nausea (27%). Sore throat was associated with COVID-19 negativity (60% vs 32% in COVID-19–positive patients). Fever was the most common presenting symptom (54%), whereas 22% reported anosmia at initial presentation of COVID-19–positive illness.

Compared to other symptoms of COVID-19 infection, loss of smell and taste showed the largest magnitudes of association with COVID-19 positivity (anosmia: OR 10.9; 95% CI, 5.6-21.0; ageusia: OR 11.9; 95% CI, 6.1-23.2, Table 2, left column). Multivariable logistic regression adjusting for myalgia/arthralgia, fatigue, fever, nausea, and sore throat demonstrated that both smell and taste impairment independently associated with COVID-19 positivity (anosmia: aOR 10.9; 95% CI, 5.08-23.5; taste: aOR 10.2; 95% CI, 4.74-22.1, Table 2, middle and right columns). Conversely, sore throat was independently associated with COVID-19 negativity, with COVID-19–negative patients being 4-fold to 5-fold more likely to report sore throat as a symptom (aOR 0.23; 95% CI, 0.11-0.50). Beyond smell loss, taste loss, and sore throat, only nausea was found to be consistently and independently associated with COVID-19 positivity. None of the evaluated comorbidities listed in Table 1 associated with COVID-19 status.

Patterns of COVID-19–related olfactory/gustatory impairment demonstrate a profound to complete anosmia/ageusia, with a significant majority achieving spontaneous improvement (Figs. 1 and 2). Notably, the degree of COVID-19–related anosmia and ageusia correlate closely in affected individuals. No patients in this study received

TABLE 1. Baseline characteristics*

	COVID-19–positive (n = 59) n (%)	COVID-19–negative (n = 203) n (%)	p
Age group[a]			0.19
18–29 years	10 (17.0)	26 (12.9)	
30–39 years	11 (18.6)	67 (33.2)	
40–49 years	17 (28.8)	39 (19.3)	
50–59 years	9 (15.3)	36 (17.8)	
60–69 years	7 (11.9)	19 (9.4)	
70–79 years	5 (8.5)	10 (5.0)	
≥80 years	0	5 (2.5)	
Gender[b]			0.033
Male	29 (49.2)	69 (34.0)	
Female	29 (49.2)	132 (65.0)	
Gender diverse	1 (1.7)	0	
Improvement of illness[c]			0.66
No	8 (13.6)	38 (18.7)	
Yes	50 (84.8)	162 (79.8)	
Hospital admission[d]			0.98
No	54 (93.1)	186 (93.0)	
Yes	4 (6.9)	14 (7.0)	
Any symptoms			
Fatigue	48 (81.4)	116 (57.1)	0.001
Ageusia	42 (71.2)	35 (17.2)	<0.001
Fever	41 (69.5)	87 (42.9)	<0.001
Anosmia	40 (67.8)	33 (16.3)	<0.001
Cough	39 (66.1)	156 (76.9)	0.096
Headache	39 (66.1)	99 (48.8)	0.019
Myalgia/arthralgia	37 (62.7)	65 (32.0)	<0.001
Dyspnea	32 (54.2)	88 (43.4)	0.14
Diarrhea	28 (47.5)	50 (24.6)	0.001
Nasal obstruction	28 (47.5)	91 (44.8)	0.72
Sore throat	19 (32.2)	122 (60.1)	<0.001
Rhinorrhea	18 (30.5)	83 (40.9)	0.15
Nausea	16 (27.1)	23 (11.3)	0.004
Presenting symptoms			
Fatigue	25 (42.4)	62 (30.5)	0.089
Ageusia	12 (20.3)	10 (4.9)	<0.001
Fever	32 (54.2)	53 (26.1)	<0.001

(Continued)

TABLE 1. Continued

	COVID-19–positive (n = 59) n (%)	COVID-19–negative (n = 203) n (%)	*p*
Anosmia	13 (22.0)	9 (4.4)	<0.001
Cough	21 (35.6)	104 (51.2)	0.034
Headache	25 (42.4)	40 (19.7)	<0.001
Myalgia/arthralgia	20 (33.9)	39 (19.2)	0.017
Dyspnea	7 (11.9)	47 (23.2)	0.059
Diarrhea	5 (8.5)	16 (7.9)	0.88
Nasal obstruction	11 (18.6)	43 (21.2)	0.67
Sore throat	10 (17.0)	92 (45.3)	<0.001
Rhinorrhea	6 (10.2)	40 (19.7)	0.09
Nausea	3 (5.1)	8 (3.9)	0.7
Comorbidities			
Allergic rhinitis	20 (33.9)	77 (37.9)	0.57
Other immunosuppressed state	9 (15.3)	32 (15.8)	0.92
Hypertension	8 (13.6)	30 (14.8)	0.82
Diabetes	5 (8.5)	15 (7.4)	0.78
Cardiac disease	3 (5.1)	13 (6.4)	0.71
Chronic lung disease	3 (5.1)	31 (15.3)	0.04
Cancer	2 (3.4)	10 (4.9)	0.62
Sinus disease	2 (3.4)	20 (9.9)	0.12
History of head trauma	1 (1.7)	13 (6.4)	0.16
Neurologic disease	0	6 (3.0)	0.18

[*]Differences in self-reported clinical feature distributions across COVID-19–positive and COVID-19–negative patients were evaluated by chi-square test with *p* values reported in the right column.
[a]One patient did not answer question on age group. All other reported results based on 100% response rates.
[b]Two patients did not answer question on gender. All other reported results based on 100% response rates.
[c]Four patients did not answer question on improvement of illness. All other reported results based on 100% response rates.
[d]Four patients did not answer question on hospital admission. All other reported results based on 100% response rates.

treatment for olfactory or gustatory loss. Among COVID-19–positive subjects who experienced smell loss, 29 of 40 (72.5%) reported improvement at time of survey (18% by <1 week, 37.5% by 1 to 2 weeks, 18% by 2 to 4 weeks).

The majority of COVID-19–positive patients had improvement of olfaction and taste that temporally correlated with clinical resolution of illness (Fig. 3A). Seventy-four percent (28/38, 2 failed to respond) of affected patients reported both improvement of olfactory dysfunction and overall illness symptoms. Those who did not experience improvement in smell also had not felt improvement in other clinical symptoms. Four patients reported clinical improvement without olfactory improvement; however, these patients were less than 2 weeks from onset of symptoms. Similarly, of those who reported no improvement of smell loss, 82% were diagnosed <2 weeks prior (Fig. 3B).

Discussion

This study shows the prevalence and unique presentation of chemosensory impairment in COVID-19–positive compared to COVID-19–negative individuals, both presenting with similar influenza-like symptoms. We found a significant association between smell/taste loss and COVID-19 infection because these chemosensory impairments were at least 10-fold more common in COVID-19–positive cases. Of those who reported olfactory dysfunction, the loss was typically profound rather than mild. Despite the slightly higher reported incidence of ageusia compared to anosmia, we know that loss of taste is linked with one's loss of smell and the differences in reporting can be attributed to the few patients with baseline rhinosinusitis-induced anosmia.

We have also shown that most patients reported improvement of smell and taste at the time of the survey,

TABLE 2. Self-reported clinical feature associations with COVID-19-positivity*

Parameter	Univariable regression OR (95% CI)	p	Multivariable regression aOR (95% CI)[a]	p	Multivariable regression aOR (95% CI)[b]	p
Age group (years)	0.72 (0.33–1.60)	0.43				
Gender	0.53 (0.30–0.96)	0.036				
Improvement of illness	1.47 (0.64–3.35)	0.36				
Hospital admission	0.98 (0.31–3.11)	0.98				
Any symptoms						
Ageusia[c]	11.86 (6.06–23.19)	<0.001	—	—	10.23 (4.74–22.09)	<0.001
Anosmia[c]	10.85 (5.60–21.01)	<0.001	10.92 (5.08–23.53)	<0.001	—	—
Myalgia/arthralgia[c]	3.57 (1.95–6.54)	<0.001	1.74 (0.79–3.84)	0.17	1.53 (0.71–3.33)	0.28
Fatigue[c]	3.27 (1.61–6.67)	0.001	1.53 (0.61–3.84)	0.37	1.23 (0.50–3.04)	0.66
Fever[c]	3.03 (1.63–5.65)	<0.001	1.55 (0.71–3.40)	0.27	1.67 (0.77–3.60)	0.19
Nausea[c]	2.91 (1.42–5.98)	0.004	2.86 (1.16–7.01)	<0.001	2.71 (1.07–6.83)	0.035
Diarrhea	2.76 (1.51–5.05)	0.001	—	—	—	—
Headache	2.05 (1.12–3.75)	0.02	—	—	—	—
Dyspnea	1.55 (0.86–2.77)	0.064	—	—	—	—
Nasal obstruction	1.11 (0.62–1.99)	0.72	—	—	—	—
Rhinorrhea	0.63 (0.34–1.18)	0.096	—	—	—	—
Cough	0.59 (0.31–1.10)	0.098	—	—	—	—
Sore throat[c]	0.32 (0.17–0.58)	<0.001	0.20 (0.09-0.44)	<0.001	0.23 (0.11–0.50)	<0.001
Presenting symptoms						
Fatigue	1.67 (0.92–3.04)	0.091				
Ageusia	4.93 (2.01–12.10)	<0.001				
Fever	3.35 (1.84–6.11)	<0.001				
Anosmia	6.09 (2.46–15.11)	<0.001				
Cough	0.53 (0.29–0.96)	0.036				
Headache	3.00 (1.61–5.58)	0.001				
Myalgia/arthralgia	2.16 (1.13–4.10)	0.019				
Dyspnea	0.45 (0.19–1.05)	0.064				
Diarrhea	1.08 (0.38–3.09)	0.88				
Nasal obstruction	0.85 (0.41–1.78)	0.67				
Sore throat	0.25 (0.12–0.51)	<0.001				
Rhinorrhea	0.46 (0.19–1.15)	0.096				
Nausea	1.31 (0.34–5.09)	0.70				

*Associations of self-reported clinical feature associations to COVID-19-status were tested using univariable (left column, reporting unadjusted ORs) and multivariable (middle and right columns, reporting aORs) logistic regression models. Separate multivariable regression models were conducted for anosmia (middle column) and ageusia (right column), given the observed collinearity of these variables.
[a]Multivariable regression including anosmia.
[b]Multivariable regression including ageusia.
[c]Variables included in the multivariable regression analysis.
aOR = adjusted odds ratio; OR = odds ratio; CI = confidence interval; COVID-19 = coronavirus 2019.

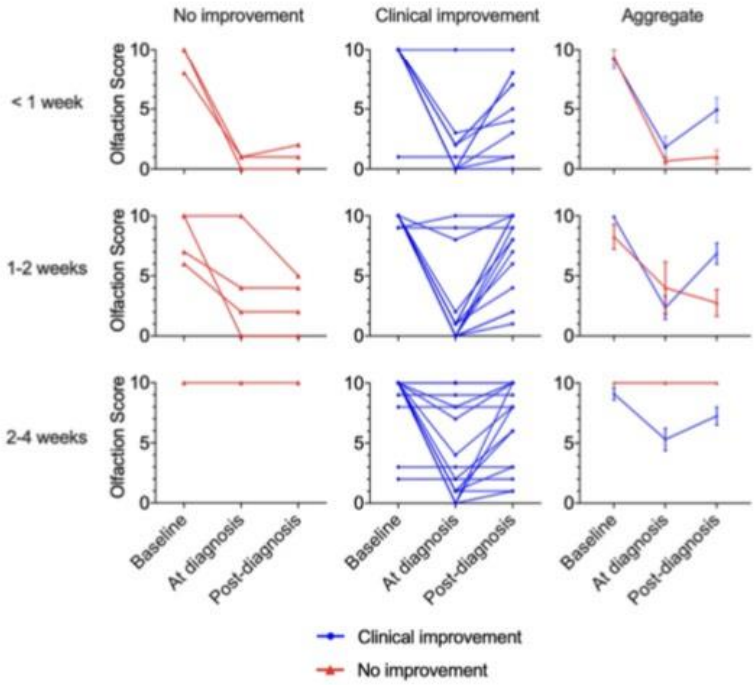

FIGURE 1. Temporal association of olfactory score and COVID-19 testing. Spaghetti plot of all COVID-19–positive individuals (n = 59) reporting olfactory scores (0: no sense of smell, 10: normal sense of smell) at baseline, at time of COVID-19 diagnosis, and at time of survey completion (post–COVID-19 diagnosis either <1 week, 1 to 2 weeks, or 2 to 4 weeks). Rows represent time elapsed between testing positive for COVID-19 and completion of survey. The left and middle columns reflect patient stratification into groups who failed to improve (red lines, left column) and those who achieved improvement/resolution of clinical symptoms (blue lines, middle column) at the time of survey completion. The right column displays aggregated results (mean, SEM) stratified by clinical improvement. COVID-19 = coronavirus 2019; SEM = standard error of the mean.

typically less than 2 weeks postdiagnosis. Similarly, the overall symptoms of disease improved or resolved during that time frame. In select cases (10%), patients reported early resolution of clinical symptoms without return of olfaction. It is possible that some of these individuals may regain sense of smell with more time because 82% of them had been tested for COVID-19 less than 2 weeks prior. Overall, these findings may offer reassurance that patients with ambulatory COVID-19 infection and associated anosmia/hyposmia may recover olfactory function within weeks paralleling resolution of other disease-related symptoms.

Of the COVID-19–positive respondents in this study, most did not require hospitalization, and none required intubation, suggesting that a relatively mild subset of COVID-19 infection was captured. This is in contrast to the hospital-based survey of COVID-19 infections by Giacomelli et al.[3] that reported rates of chemosensory loss at one-half the level of our subjects. This suggests that ambulatory and inpatient COVID-19 cases may follow fundamentally different clinical courses. We hypothesize that perhaps ambulatory cases are in part the result of nasal-centric viral spread, whereas patients requiring hospitalization may be experiencing a more pulmonary-centric viral infection leading to increased rate of respiratory failure and need for hospitalization. Future studies are warranted to investigate this hypothesis because, if found to be true, beyond potential screening markers for COVID-19 infection positivity, anosmia/ageusia may carry some prognostic potential on severity of disease.

Postviral anosmia is a common cause of smell loss in adults and is known to be associated with many human viral strains, including other coronaviruses.[4] Early studies evaluating mechanisms of SARS-CoV2–mediated olfactory loss have suggested neurotrophic targeting of olfactory neurons vs infection of non-neural olfactory epithelial cells.[5,6] The short-lived COVID-19–related olfactory loss found in our study favors a model in which SARS-CoV2 targets the olfactory epithelium, which can rapidly regenerate and repair after viral clearance.

Larger-scale studies on epidemiologically balanced datasets are warranted to accurately determine the overall incidence and prevalence of COVID-19–related anosmia/hyposmia, and to determine its predictive value for COVID-19 infection. This study is limited by a

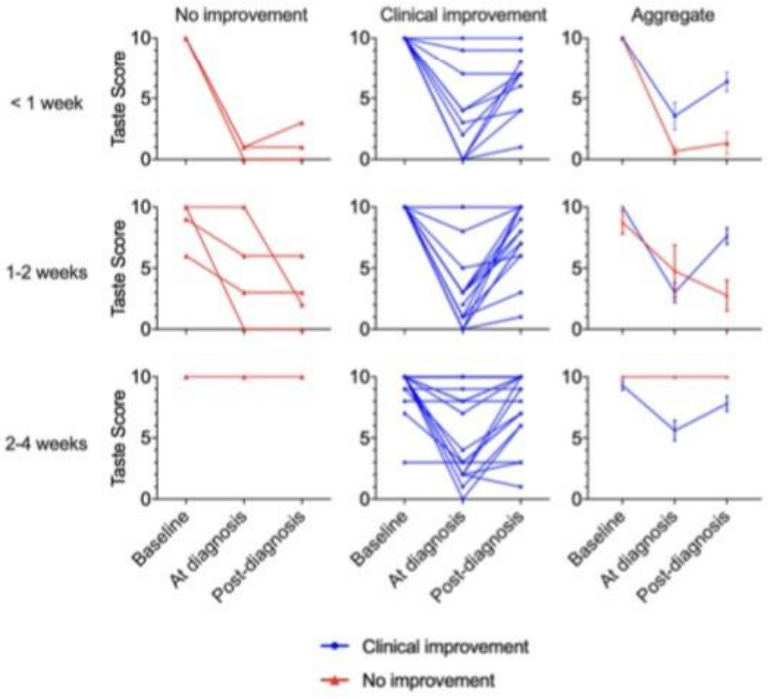

FIGURE 2. Temporal association of taste score and COVID-19 testing. Spaghetti plot of all COVID-19–positive individuals (n = 59) reporting taste scores (0: no sense of taste, 10: normal sense of taste) at baseline, at time of COVID-19 diagnosis, and at time of survey completion (post–COVID-19 diagnosis either <1 week, 1 to 2 weeks, or 2 to 4 weeks). Rows represent time elapsed between testing positive for COVID-19 and completion of survey. The left and middle columns reflect patient stratification into groups who failed to improve (red lines, left column) and those who achieved improvement/resolution of clinical symptoms (blue lines, middle column) at the time of survey completion. The right column displays aggregated results (mean, SEM) stratified by clinical improvement. COVID-19 = coronavirus 2019; SEM = standard error of the mean.

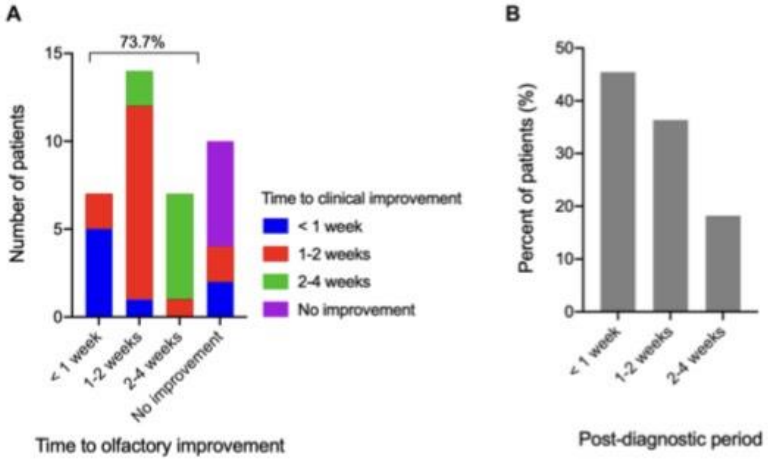

FIGURE 3. Temporal relationship between olfactory improvement and clinical improvement following COVID-19 infection. (A) Histogram demonstrating the reported time to improvement in COVID-19–positive subjects with olfactory loss and its relationship to patient-reported time to overall clinical improvement (n = 38, 2 subjects did not answer time to clinical improvement). (B) Histogram demonstrating the time post–COVID-19 diagnosis (approximate time elapsed since testing positive) in subjects who reported no improvement of smell loss (n = 11); 81.8% were diagnosed <2 weeks prior. COVID-19 = coronavirus 2019.

short sampling period at a single institution, as well as the subjective assessment used to determine smell/taste impairment. Furthermore, by surveying respondents after COVID-19 testing, we risk post hoc interpretations of smell and taste loss through their knowledge of their diagnosis, a potential recall bias especially in the context of pervasive anecdotal reports of COVID-19–related anosmia. Specifically, it remains possible that patients with smell loss in the COVID-19–positive group were more likely to respond based on media reporting of smell loss and/or desire to share their experience, as compared to the COVID-19–negative group. However, the comparison of clinical characteristics and outcomes between the COVID-19–positive and COVID-19–negative cohorts was valuable in determining true associations because all individuals were deemed persons under investigation (PUIs) prior to study enrollment and demonstrated minor differences in baseline characteristics beyond COVID19 status. One must also consider the sensitivity and potential false-negativity of the PCR-based COVID-19 assays. Two of our subjects had previously tested negative for COVID-19 infection and subsequent testing resulted in a positive test.

In this study, olfaction was evaluated using a subjective olfaction score of 1 to 10 because a true visual analog scale (VAS) was unable to be performed through the online survey platform. It has been previously shown that compared to more objective batteries of olfactory testing, subjective reporting of sense of smell is specific but not sensitive.[7] Typically, people do not recognize their loss of smell and thus tend to underreport smell loss. However, we must weigh this possibility against the potential information bias of COVID-19 test positivity. Future studies using well-validated instruments of olfaction, will be important to corroborate these patient-reported subjective assessments of olfactory loss.

Conclusion

There is a strong association of olfactory and gustatory impairment with COVID-19 infection and a temporal relationship of improvement of these symptoms with resolution of overall clinical illness in this predominantly ambulatory population. This study offers support for using smell/taste loss as a symptom for heightened screening of COVID-19 infections in an effort to decrease the risk of disease transmission from mildly symptomatic cases.

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RHINOLOGY

Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study

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Abstract

Objective To investigate the occurrence of olfactory and gustatory dysfunctions in patients with laboratory-confirmed COVID-19 infection.

Methods Patients with laboratory-confirmed COVID-19 infection were recruited from 12 European hospitals. The following epidemiological and clinical outcomes have been studied: age, sex, ethnicity, comorbidities, and general and otolaryngological symptoms. Patients completed olfactory and gustatory questionnaires based on the smell and taste component of the National Health and Nutrition Examination Survey, and the short version of the Questionnaire of Olfactory Disorders-Negative Statements (sQOD-NS).

Results A total of 417 mild-to-moderate COVID-19 patients completed the study (263 females). The most prevalent general symptoms consisted of cough, myalgia, and loss of appetite. Face pain and nasal obstruction were the most disease-related otolaryngological symptoms. 85.6% and 88.0% of patients reported olfactory and gustatory dysfunctions, respectively. There was a significant association between both disorders ($p < 0.001$). Olfactory dysfunction (OD) appeared before the other symptoms in 11.8% of cases. The sQO-NS scores were significantly lower in patients with anosmia compared with normosmic or hyposmic individuals ($p = 0.001$). Among the 18.2% of patients without nasal obstruction or rhinorrhea, 79.7% were hyposmic or anosmic. The early olfactory recovery rate was 44.0%. Females were significantly more affected by olfactory and gustatory dysfunctions than males ($p = 0.001$).

Conclusion Olfactory and gustatory disorders are prevalent symptoms in European COVID-19 patients, who may not have nasal symptoms. The sudden anosmia or ageusia need to be recognized by the international scientific community as important symptoms of the COVID-19 infection.

Keywords Coronavirus · COVID · COVID-19 · SARS-CoV-2 · Anosmia · Smell · Hyposmia · Dysgeusia · Taste · Loss · Gustatory · Olfactory · Olfaction · Infection · ENT

Introduction

The coronavirus disease 2019 (COVID-19) is an ongoing viral pandemic that emerged from East Asia and quickly spread to the rest of the world [1]. This infection is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is so far responsible for more than 15,000 deaths worldwide [2]. Human-to-human transmission is characterized by a troubling exponential rate, which

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has led to steep curves of onset in many areas [3]. According to the clinical studies from Asia, the most prevalent symptoms consist of fever, cough, dyspnea, sputum production, myalgia, arthralgia, headache, diarrhea, rhinorrhea, and sore throat [4, 5]. The spread of the COVID-19 infection in Europe has highlighted a new atypical presentation of the disease: patients with olfactory and gustatory dysfunctions. The occurrence of smell dysfunction in viral infections is not new in otolaryngology. Many viruses may lead to olfactory dysfunction (OD) through an inflammatory reaction of the nasal mucosa and the development of rhinorrhea; the most familiar agents being rhinovirus, parainfluenza Epstein–Barr virus, and some coronavirus [6, 7]. However, olfactory dysfunction linked to COVID-19 infection seems particular as it is not associated with rhinorrhea.

Over the past few weeks, some European otolaryngologists observed that many patients infected by SARS-CoV-2 presented with severe olfactory and gustatory dysfunctions without rhinorrhea or nasal obstruction. At baseline, no COVID-19 was suspected in some of these patients, because they had no fever, cough, or other systemic complaints. Faced with numerous reports from otolaryngologists all around Europe, the Young-Otolaryngologists of the International Federation of Oto-rhino-laryngological Societies (YO-IFOS) decided to conduct an international epidemiological study to characterize olfactory and gustatory disorders in infected patients.

The aim of this study is to investigate and characterize the occurrence of olfactory and gustatory disorders in patients with laboratory-confirmed COVID-19 infection.

Materials and methods

Three ethics committees approved the current study protocol (HAP2020-011; CHUSP20032020; EpiCURA-2020-2303). Patients were invited to participate and the informed consent was obtained.

Subjects and setting

The clinical data of patients with laboratory-confirmed COVID-19 infection have been collected from four Belgian Hospitals (CHU Saint-Pierre, Brussels; CHU Ambroise Paré, Mons; EpiCURA, Baudour; EpiCURA, Ath), and University of Mons (Belgium). In addition to these ones, many other patients, infected physicians and nurses have been voluntarily enrolled in the study from the following hospitals: Foch Hospital (Paris, France); Ambroise Paré Hospital (AP-HP, Paris), CHU Ambroise Paré (Mons, Belgium), Hospital Universitario Donostia (Donostia, Spain); Hospital Universitario Santiago de Compostela (Santiago de Compostela, Spain); Morgagni Pierantoni Hospital (Forli, Italy), Department of Neuroscience, Audiology Unit (Padova University, Treviso, Italy), and Medical Departments of the Università degli Studi della Campania 'Luigi Vanvitelli' (Naples, Italy).

The following inclusion criteria have been considered: adult (> 18 years old); laboratory-confirmed COVID-19 infection (reverse transcription polymerase chain reaction, RT-PCR); native speaker patients, and patients clinically able to fulfill the questionnaire. The following exclusion criteria have been considered: patients with olfactory or gustatory dysfunctions before the epidemic; patients without a laboratory-confirmed COVID-19 infection diagnosis; patients who were in the intensive-care unit at the time of the study (due to their health status). Thus, we mainly included mild-to-moderate COVID-19 patients, defined as patients without need of intensive cares. Since we focused on the prevalence of olfactory and gustatory disorders, clinical presentation was not considered in as inclusion criteria.

Clinical outcomes

Clinical data have been prospectively collected during the ear, nose, and throat (ENT) consultation; in the patient's room; or over the phone for house-bound patients or infected health professionals. The data were also collected through an online form for house-bound patients. The online questionnaire was created with Professional Survey Monkey (San Mateo, CA, USA), so that each participant could complete the survey only once.

The selection of the relevant epidemiological and clinical features composing the questionnaire was carried out by the COVID-19 Task Force of YO-IFOS, which includes otolaryngologists from North America, Europe, and Asia [8]. Experts analyzed the epidemiological publications of the current and the previous coronavirus infections, including SRAS-CoV-1 (2002); Middle-East respiratory syndrome-related coronavirus infection (MERS-CoV, 2012), and the COVID-19 infection. From the literature, ten experts (JRL, SS, MH, JHS, PL, TA, LD, FEA, CCH, and CMCE) developed the questionnaire, which consisted of four general questions (age, sex, ethnicity, and date of diagnosis); three general clinical questions (comorbidities, general, and ENT symptoms associated with COVID-19 infection); seven questions about olfactory function; four questions investigating

gustatory function; and one question about the treatment of the COVID-19 infection. All patients were asked to complete the short version of the Questionnaire of Olfactory Disorders-Negative Statements (sQOD-NS) [9]. The questionnaire has been translated into Spanish, Italian, and English by two native speaker otolaryngologists for each language.

Olfactory and gustatory outcomes

The occurrence of anosmia or hyposmia has been identified in the questionnaire. The impact of olfactory dysfunction on the quality of life (QoL) of patients has been assessed through the validated sQOD-NS (Appendix 1) [9]. This is a seven-item patient-reported outcome questionnaire including social, eating, annoyance, and anxiety questions. Each item is rated on a scale of 0–3, with higher scores reflecting better olfactory-specific QoL. The total score ranges from 0 (severe impact on QoL) to 21 (no impact on QoL) [9]. The rest of the olfactory and gustatory questions were based on the smell and taste component of the National Health and Nutrition Examination Survey [10]. This population survey was implemented by the Centers for Disease Control and Prevention to continuously monitor the health of adult citizens in the United States through a nationally representative sample of 5000 persons yearly [10]. The questions have been chosen to characterize the variation, timing, and associated symptoms of both olfactory and gustatory dysfunctions, and, therefore, they suggest a potential etiology. Note that we assessed the mean recovery time of olfaction through four defined propositions: 1–4 days; 5–8 days; 9–14 days; and > 15 days.

Referring to the studies that have demonstrated that the viral load was significantly decreased after 14 days [11], we assessed the short-term olfaction non-recovery rate on patients exhibiting double criteria: an onset of the infection > 14 days before the assessment and the lack of general symptoms at the time of the evaluation.

Statistical methods

Statistical Package for the Social Sciences for Windows (SPSS version 22,0; IBM Corp, Armonk, NY, USA) was used to perform the statistical analyses. The potential associations between epidemiological, clinical and olfactory and gustatory outcomes have been assessed through cross-tab generation between two variables (binary or categorical variables) and Chi-square test. Incomplete responses were excluded from analysis. The differences in sQOD-NS scores between patients regarding the olfactory dysfunction were made through the Kruskal–Wallis test. A level of $p < 0.05$ was used to determine statistical significance.

Results

A total of 417 patients completed the study. The mean age of patients was 36.9 ± 11.4 years (range 19–77). There were 263 females and 154 males. The following ethnicities composed the cohort: European (93.3%), South American (2.7%), Sub-Saharan African (2.2%), Black African (1.4%), Asian (0.2%), and North American (0.2%) (Table 1). The most prevalent comorbidities of patients were allergic rhinitis, asthma, high blood pressure, and hypothyroidism (Fig. 1). The mean time between the onset of the infection and the evaluation was 9.2 ± 6.2 days. At the time of the study, 34.5% of patients were in the acute phase of the infection, whereas the rest of the patients did not yet have general symptoms.

Clinical outcomes

The general symptoms of patients during the infection are described in Fig. 2. Cough, myalgia, loss of appetite, diarrhea, fever, headache, and asthenia were the most prevalent symptoms, accounting for more than 45% of patients. The otolaryngological symptoms most related to the infection are reported in Table 2.

Olfactory outcomes

A total of 357 patients (85.6%) had olfactory dysfunction related to the infection. Among them, 284 (79.6%) patients were anosmic and 73 (20.4%) were hyposmic. Phantosmia and parosmia concerned 12.6% and 32.4% of patients during the disease course, respectively. The olfactory dysfunction appeared before (11.8%), after (65.4%) or at the same time as the appearance of general or ENT symptoms (22.8%). Note that 9.4% of patients did not remember the time of onset of olfactory dysfunction and, therefore, were not considered for the percentage evaluation.

Considering the 247 patients with a clinically resolved infection (absence of general and ENT symptoms), the olfactory dysfunction persisted after the resolution of other symptoms in 63.0% of cases. The mean time between the onset of the disease and the assessment of this group of patients was 9.77 ± 5.68 days.

The short-term olfaction recovery rate, which was assessed in 59 clinically cured patients, was 44.0%. The different recovery times of the olfactory function of patients who reported a recovery of the olfactory function are available in Fig. 3. In total, 72.6% of these patients recovered olfactory function within the first 8 days following the resolution of the disease. Among the patients who reported anosmia, then, excluding hyposmic patients, the olfactory

Table 1 Demographic and epidemiological characteristics of patients

Characteristics	Mean ± SD	Range
Age (years old)	36.9 ± 11.4	19–77
Characteristics	Number	Percentages
Gender		
Male	154	36.9
Female	263	63.1
Ethnicity		
European	389	93.3
Asian	1	0.2
Black African	6	1.4
Sub-Saharan African	9	2.2
North American	1	0.2
South American	11	2.6
Oceanian	0	0.0
Addictions		
Non-smoker	361	86.6
Mild smoker (1–10 cigarettes daily)	40	9.6
Moderate smoker (11–20 cigarettes daily)	16	3.8
Heavy smoker (> 20 cigarettes daily)	0	0.0
Allergic patients	85	20.4

SD standard deviation

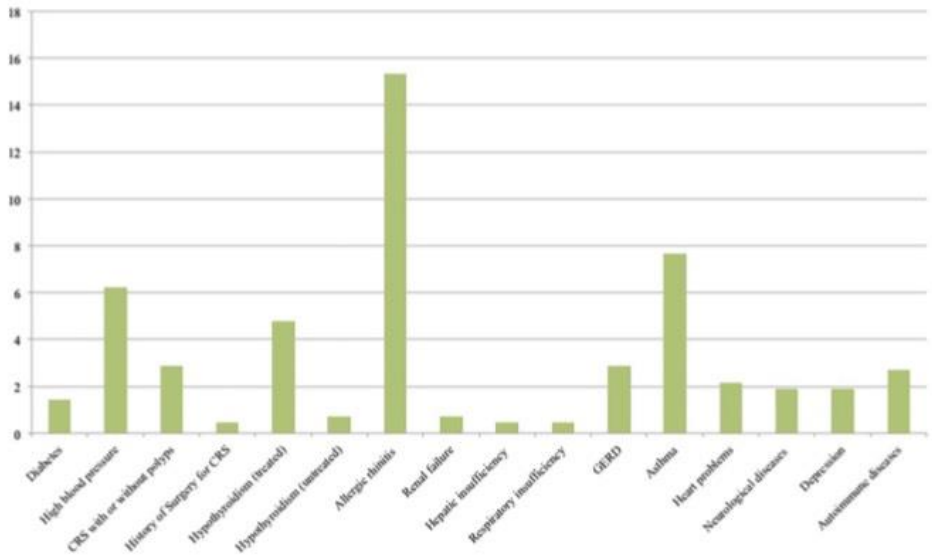

Fig. 1 Comorbidities of COVID-19 patients. The ordinate axis consists of percentages of patients with comorbidities in the cohort. Respiratory insufficiency consists of COPD, emphysema, fibrosis, or other chronic disease associated with a respiratory insufficiency. Neurological diseases include Parkinson disease, myasthenia, multiple sclerosis, and all degenerative diseases. *COPD* chronic obstructive pulmonary disease, *CRS* chronic rhinosinusitis, *GERD* gastroesophageal reflux disease

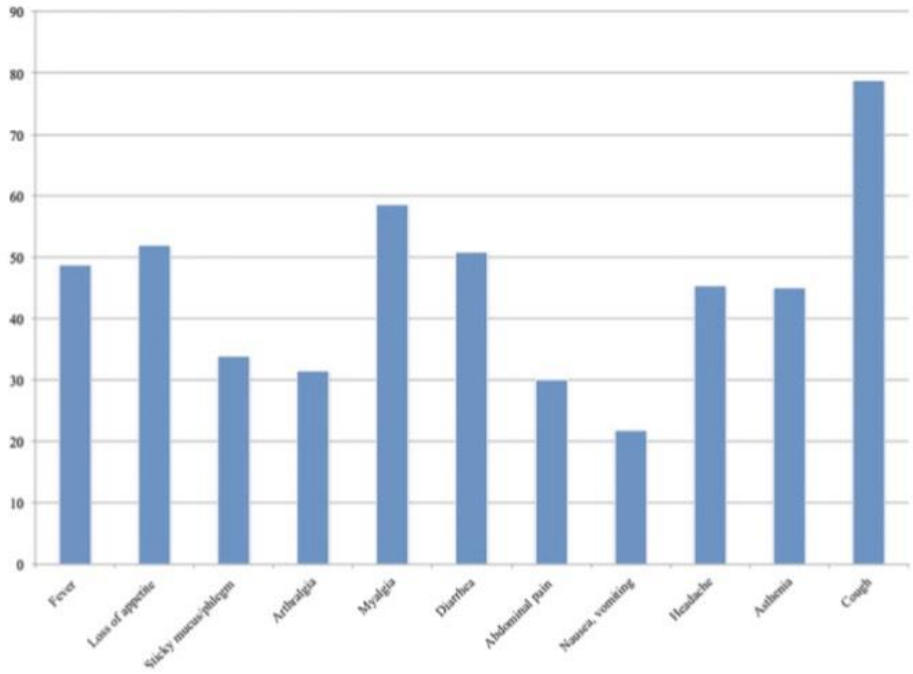

Fig. 2 General symptoms associated with COVID-19 infection. The ordinate axis consists of percentages of patients with such symptoms associated with the infection

Table 2 Otolaryngological complaints associated with COVID-19 Infection

	Not related		Somewhat related		Highly related
	(0)	(1)	(2)	(3)	(4)
Nasal obstruction	131 (31.49)	91 (21.88)	77 (18.51)	67 (16.11)	50 (12.02)
Rhinorrhea	154 (37.11)	122 (29.40)	81 (19.52)	40 (9.64)	18 (4.34)
Postnasal drip	203 (48.80)	97 (23.32)	61 (14.66)	26 (6.25)	29 (6.97)
Sore throat	192 (46.15)	96 (23.08)	57 (13.70)	38 (9.13)	33 (7.93)
Face pain/heaviness	198 (47.60)	66 (15.87)	59 (14.18)	39 (9.38)	54 (12.98)
Ear pain	310 (74.52)	45 (10.82)	32 (7.69)	16 (3.85)	13 (3.13)
Dysphagia	24 (22.64)	40 (37.74)	24 (22.64)	11 (10.38)	7 (6.60)
Dyspnea	218 (52.40)	83 (19.95)	61 (14.66)	35 (8.41)	19 (4.57)

Percentages are in brackets. Patients had to rate each of the following symptoms in terms of their relationship with your COVID-19 infection (scale: 0–4, where 0 = not related, 4 = highly related)

function recovered throughout the 8 first days following the resolution of the disease in 67.8% of cases (Fig. 3).

In the present study, 76 patients did not suffer from nasal obstruction or rhinorrhea (18.2%). Among them, 20.3% did not report olfactory dysfunction, whereas 66.2% and 13.5% suffered from anosmia and hyposmia, respectively.

The impact of olfactory dysfunction on patient QoL is reported in Table 3. Anosmic patients at the time of the evaluation had a significant lower sQOD-NS score compared with hyposmic and normosmic individuals ($p = 0.001$; Kruskal–Wallis).

Gustatory outcomes

A total of 342 patients (88.8%) reported gustatory disorders, which was characterized by impairment of the following four

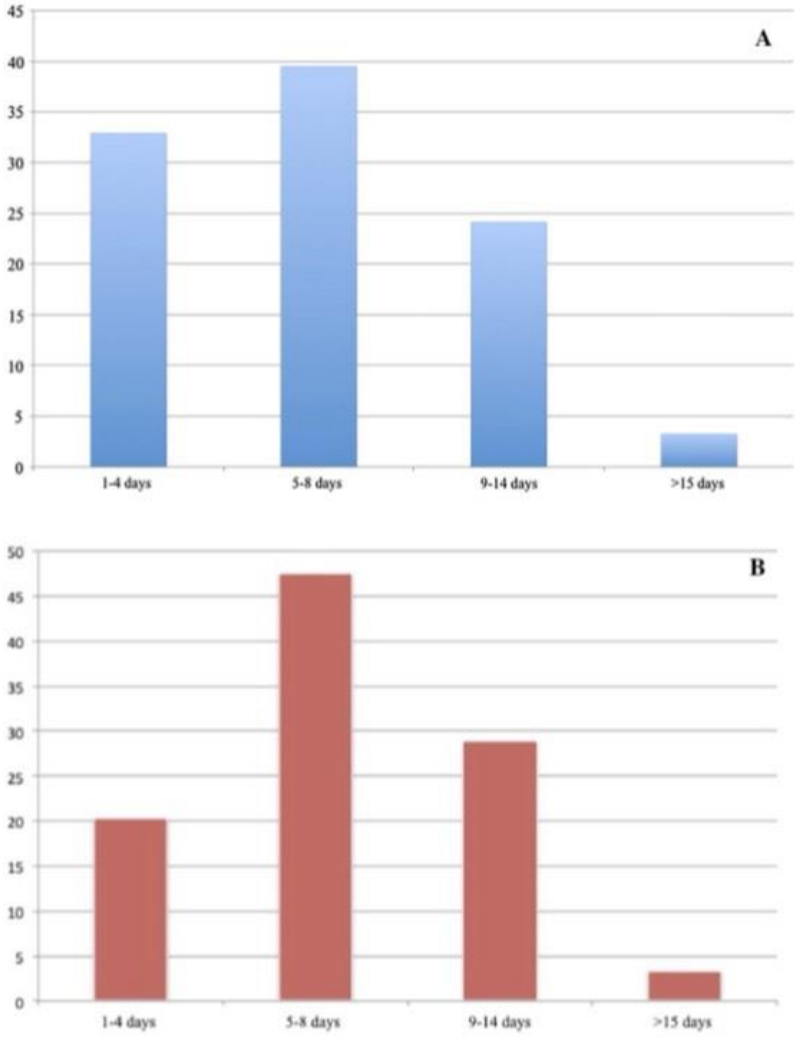

Fig. 3 Pattern of recovery time for patients with olfactory dysfunction. The ordinate axis consists of percentages of patients. The patients with hyposmia or anosmia had the following recovery times **a** 1–4 days (33.0%), 5–8 days (39.6%), 9–14 days (24.2%), and more than 15 days (3.3%). The patients with anosmia had the following recovery times **b** 1–4 days (20.3%), 5–8 days (47.5%), 9–14 days (28.8%), and more than 15 days (3.4%)

taste modalities: salty, sweet, bitter, and sour. Note that 32 patients did not remember if they had gustatory dysfunction and, therefore, they were not considered for the assessment of the gustatory disorder prevalence. The gustatory dysfunction consisted of reduced/discontinued or distorted ability to taste flavors in 78.9% and 21.1% of patients, respectively.

Among the 43 patients without gustatory dysfunction, 19 (44.2%) have no olfactory dysfunction, whereas 16 (37.2%) and 4 (9.3%) patients had anosmia or hyposmia.

The olfactory and gustatory disorders were constant and unchanged over the days in 72.8% of patients, whereas they fluctuated in 23.4% of patients. Among the patients who reported gustatory and olfactory disorders, 3.8% revealed that these disorders occurred during their rhinorrhea or nasal obstruction episodes.

Among the cured patients who had residual olfactory and/or gustatory dysfunction, 53.9% had isolated olfactory dysfunction, 22.5% had isolated gustatory dysfunction, and 23.6% had both olfactory and gustatory dysfunctions.

Olfactory and gustatory outcome associations

There was no significant association between comorbidities and the development of olfactory or gustatory dysfunctions.

Table 3 Short version of questionnaire of olfactory disorders-negative statements of patient

Short version QOD-NS items	Anosmia	Hyposmia	No LS
Changes in my sense of smell isolate me socially	1.68 ± 0.91*	2.34 ± 0.75	2.53 ± 0.65
The problems with my sense of smell have a negative impact on my daily social activities	1.37 ± 0.93*	2.11 ± 0.84	2.56 ± 0.69
The problems with my sense of smell make me more irritable	1.46 ± 0.92*	2.21 ± 0.82	2.64 ± 0.59
Because of the problems with my sense of smell, I eat out less	1.30 ± 1.09*	2.12 ± 0.99	2.31 ± 1.04
Because of the problems with my sense of smell, I eat less than before (loss of appetite)	1.00 ± 0.88*	1.59 ± 0.97	2.36 ± 0.90
Because of the problems with my sense of smell, I have to make more effort to relax	1.67 ± 0.88*	2.91 ± 0.79	2.61 ± 0.60
I'm afraid I'll never be able to get used to the problems with my sense of smell.	0.73 ± 0.86*	1.90 ± 1.06	2.06 ± 1.19
Short version QOD-NOS total score	9.15 ± 4.60*	14.44 ± 4.59	13.60 ± 8.17

sQOD-NS is a seven-item patient-reported outcome questionnaire including social, eating, annoyance, and anxiety questions. Each item is rated on a scale of 0–3, with higher scores reflecting better olfactory-specific QOL. The total score ranges from 0 (severe impact on QoL) to 21 (no impact on QoL) [9]. The item and total scores of sQOD-NS significantly differ between patients with anosmia at the time of the assessment, and those with hyposmia or without olfactory dysfunction (*$p = 0.001$)

LS loss of smell, *sQOD-NS* Short version of Questionnaire of Olfactory Disorders-Negative Statements

Olfactory dysfunction was not significantly associated with rhinorrhea or nasal obstruction. There was a significant positive association between olfactory and gustatory dysfunctions ($p < 0.001$). The statistical analysis identified a significant association between the fever and the anosmia ($p = 0.014$). The females would be proportionally more affected by hyposmia or anosmia compared with males ($p < 0.001$). Similar results were found for gustatory dysfunction ($p = 0.001$, Mann–Whitney U test).

Treatments of COVID-19 patients

The following general treatments have been considered for patients with the COVID-19 infection: paracetamol (62.4%); non-steroidal anti-inflammatory drugs (9.8%); nasal saline irrigations (9.6%); Chloroquine (7.9%); mucolytics (5.0%); and oral corticosteroids (1.4%, with concomitant antibiotics) (Fig. 4). The treatments that have been most used for olfactory dysfunction were nasal saline irrigations (16.7%); nasal corticosteroids (8.1%), oral corticosteroids (2.5%), and others (2.5%, e.g., vitamins, non-corticoid decongestants, and trace elements) (Fig. 4). Gustatory dysfunction was treated in 1.4% of patients: four patients received treatment, consisting of L-carnitine or trace elements and vitamins. Telemedicine has been used in 42.6% of patients for prescribing the treatment.

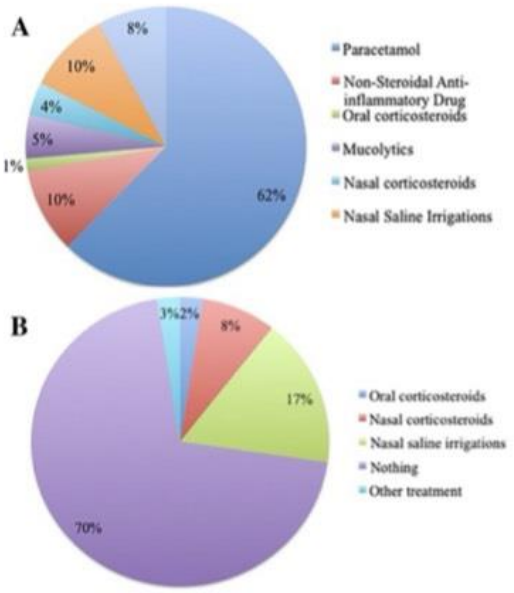

Fig. 4 Therapeutic strategies for COVID-19 infection (**a**) and olfactory dysfunction (**b**)

Discussion

Over the past few weeks, an increasing number of otolaryngologists reported sudden anosmia or hyposmia as concurrent symptoms of COVID-19 infection. In these patients, the diagnosis of COVID-19 could be missed, because these symptoms were not known to be specific. As a result, the patients were not isolated and the spread of the virus continued. In this context, the COVID-19 Task Force of the YO-IFOS has conducted this study to investigate the prevalence and the short-term evolution of both olfactory and gustatory disorders.

Based on the National Health and Nutrition Examination Survey questions, our results support that olfactory and gustatory dysfunctions are both prevalent in patients with mild-to-moderate COVID-19 infection. Thus, 85.6% of patients reported olfactory dysfunction; 79.6% of them

having anosmia. Interestingly, many profiles of patients have been identified. First, our data showed that 79.7% of patients without nasal obstruction or rhinorrhea reported hyposmia or anosmia, supporting the role of otolaryngologists as the first-line physicians for some COVID-19 patients. Second, the olfactory dysfunction may appear before, during, or after the general symptoms, with the occurrence of fever being associated with the olfactory dysfunction. There have been few studies on the occurrence of olfactory and gustatory dysfunctions in Asia, since only one study reported hyposmia as a symptom of the COVID-19 infection [12]. In the study of Mao et al., patients with peripheral nervous system symptoms attributed to COVID-19 infection, the most common the most common complaints were hypogeusia (5.6%) and hyposmia (5.1%) [12]. According to the data of the present study, the prevalence of olfactory and gustatory dysfunction is substantially higher in European COVID-19 patients. In addition to the high prevalence, physicians must keep in mind that olfactory disorder may appear before the rest of the complaints in 11.8% of cases, yielding the symptoms important for the early detection of the disease.

One of the most important questions from the otolaryngologists concerned the recovery of olfactory and gustatory functions. Although our results are still preliminary, it seems that, at least, 25.5% of patients recovered both olfactory and gustatory functions throughout the 2 weeks after the resolution of general symptoms. Considering the time to get a significant reduction of the viral load [10], we have estimated that 56% of patients have persistent olfactory dysfunction over the days following the resolution of the COVID-19 general clinical manifestations. In the same vein, some patients seemed to recover olfaction, but not taste, and vice versa. Naturally, there are short-term observations and it is reasonable to think that a large number of these patients will recover the olfactory or gustatory functions over the weeks following the disease resolution. To summarize, the present study clearly supports the recent declarations of many physicians from South Korea, Iran, Germany, Italy, Spain, France, Belgium, UK, and US that olfactory and gustatory functions may be impaired in COVID-19 patients.

The pathophysiological mechanisms leading to the olfactory and gustatory dysfunctions in the COVID-19 infection are still unknown. Coronavirus has already been identified as a family of viruses that may be associated with anosmia [6]. In 2007, Suzuki et al. demonstrated that coronavirus may be detected in the nasal discharge of patients with olfactory dysfunction. Moreover, they observed that some patients with normal acoustic rhinometry did not recover their olfaction, suggesting that nasal inflammation and related obstruction were not the only etiological factors underlying the olfactory dysfunction in viral infection.

The ability of human coronavirus to invade the olfactory bulb and, therefore, the central nervous system, is most likely a future research path for improving the knowledge about the clinical presentation of patients. From a biomolecular standpoint, viruses could infect peripheral neurons, using the cell machinery of active transport to access the central nervous system [13]. Thus, for the SARS-CoV receptor (human angiotensin-converting enzyme 2), it has been demonstrated on transgenic mice that SARS-CoV may enter the brain through the olfactory bulb, leading to rapid transneuronal spread [14]. Interestingly, authors demonstrated that the virus antigen was first detected 60–66 h post-infection and was most abundant in the olfactory bulb. Regions of the cortex (*piriform* and *infralimbic cortices*), basal ganglia (*ventral pallidum* and *lateral preoptic* regions), and midbrain (*dorsal raphe*) were also strongly infected after the virus had spread [14]; these regions are connected with the olfactory bulb. The rapid spread of SARS-CoV in the brain was also associated with significant neuronal death. In humans, autopsy samples from eight patients with SARS revealed the presence of SARS-CoV in brain samples by immunohistochemistry, electron microscopy, and real-time RT-PCR [15]. It is currently suspected that the neuroinvasive potential of SARS-CoV2 plays a key role in the respiratory failure of COVID-19 patients [16]. Medical imaging and neuropathology will certainly play an important rule to detect abnormalities in olfactory bulb, cranial nerves, and brain of COVID-19 patients.

The otolaryngological symptoms in our European cohort were particularly prevalent compared with the Asian cohorts. In their clinical series of 99 patients, Chen et al. reported four patients with rhinorrhea (4%) [17]. Then, Guan et al. reported a prevalence of nasal obstruction in 5% of patients in a cohort of 1099 patients [18]. The lack of otolaryngological complaints in Asian papers, e.g., nasal obstruction, rhinorrhea, and olfactory and gustatory dysfunctions, raises many questions. Either they did not assess the ENT complaints, or the Chinese patients had a few ENT complaints. The second hypothesis may be likely regarding previous studies. Benvenuto et al. have recently compared the complete genomes of 15 virus sequences from patients treated in different regions of China with other coronaviruses [19]. Interestingly, they observed mutations of surface proteins (spike-S-protein and nucleocapsid-N-protein), conferring stability to the viral particle. Such mutations could be clinically relevant, because the viral spike protein is responsible for virus entry into the cell, whereas the N-protein plays a pivotal role in the virus transcription and assembly efficiency. Previously, Chan et al. determined five virus sequences from patients traveling in Wuhan at the end of December 2019. This study reported identities, but less than 68%, with the SARS-related coronaviruses in specific domains. Particularly, the external subdomain region of receptor-binding domain of the S-protein only presents 39% identity, and Chan et al. propose that it might affect

the choice of human receptor and, therefore, the biological behaviour of this virus [20]. The affinity of some viruses for some tissues and individuals constitutes another area to investigate and explain the potential clinical differences between patients from different world regions. Recent studies suggested that the angiotensin converting enzyme 2 (ACE2), which is the receptor of SARS-CoV-2, could be specific to certain populations. Li et al. demonstrated that some ACE2 variants could reduce the association between human ACE2 and SARS-CoV S-protein [21]. In other words, the expression level of ACE2 in different tissues might be critical for the susceptibility, symptoms, and outcomes of COVID-19 infection [21]. Moreover, the comparison of the 15 expression quantitative trait loci (eQTLs) variants of the ACE2 gene suggested that there will be a lot of ACE2 polymorphisms and ACE2 expression levels between Asian and European populations [22]. According to these studies, it is conceivable that the diversity of ACE2 expression pattern in Asian and European populations could be an important track that needs further investigation.

Moreover, regarding our results, future studies have to explore the potential gender differences in the development of anosmia. The highest susceptibility of females to develop olfactory and gustatory dysfunctions would be related to the gender-related differences in the inflammatory reaction process [23].

The present study has several limitations. First, our patients did not benefit from specific examinations for olfactory and gustatory functions, including psychophysical tests or electrophysiological methods [24, 25]. The use of objective approaches makes sense for investigating both gustatory and olfactory functions in COVID-19 patients, and to avoid the confusion related to the retro-olfaction. These approaches would provide many responses for patients who may recover olfaction, but not taste, and vice versa. Second, our patient sample consisted of young and mild-to-moderate COVID-19 patients with little comorbidities. They may be not representative of the infected population. However, it seems ethically difficult to investigate olfaction and gustatory function in patients in life-threatening condition, such as patients in intensive-care units. Note that in this study, the majority of included patients were identified from hospital laboratory results. However, many infected physicians completed the study, and, therefore, it remains possible that many infected physicians participated to the study, because they suffered from olfactory dysfunction, although the authors have been particularly vigilant to this potential bias. Third, the lack of consistent follow-up of our patients limits us from inquiring into the recovery time of olfactory and gustatory functions, and, therefore, the rate of permanent anosmia or ageusia. Fourth, it seems difficult to identify the potential negative impact of nasal and oral corticosteroids on the clinical course of the disease; these treatments are usually used for anosmia or in common nasal complaints. In the absence of such data, the precautionary principle may prevail and, according to the guidelines of the French Society of Otolaryngology, patients must avoid corticosteroids for the treatment of the COVID-19 infection. All of these weaknesses should be considered in future studies to investigate and characterize the olfactory and gustatory functions in COVID-19 patients.

Conclusion

Since the disease is new and the virus is most likely associated with different mutations and clinical patterns, as of yet, there remain more questions than answers. This study is the first to identify both olfactory and gustatory dysfunctions as significant symptoms in the clinical presentation of the European COVID-19 infection. Based on our results, it seems that infected patients may just present olfactory and gustatory dysfunctions without other significant complaints. The sudden anosmia or ageusia need to be recognized by the international scientific community as important symptoms of the COVID-19 infection. Future epidemiological, clinical, and basic science studies must elucidate the mechanisms underlying the development of these symptoms in such a specific world population.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest.

Research involving human participants and/or animals Three ethics committees approved the current study protocol (HAP2020-011; CHUSP20032020; EpiCURA-2020-2303).

Informed consent Patients were invited to participate and the informed consent was obtained.

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Research

JAMA Neurology | Original Investigation

Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China

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IMPORTANCE The outbreak of coronavirus disease 2019 (COVID-19) in Wuhan, China, is serious and has the potential to become an epidemic worldwide. Several studies have described typical clinical manifestations including fever, cough, diarrhea, and fatigue. However, to our knowledge, it has not been reported that patients with COVID-19 had any neurologic manifestations.

OBJECTIVE To study the neurologic manifestations of patients with COVID-19.

DESIGN, SETTING, AND PARTICIPANTS This is a retrospective, observational case series. Data were collected from January 16, 2020, to February 19, 2020, at 3 designated special care centers for COVID-19 (Main District, West Branch, and Tumor Center) of the Union Hospital of Huazhong University of Science and Technology in Wuhan, China. The study included 214 consecutive hospitalized patients with laboratory-confirmed diagnosis of severe acute respiratory syndrome coronavirus 2 infection.

MAIN OUTCOMES AND MEASURES Clinical data were extracted from electronic medical records, and data of all neurologic symptoms were checked by 2 trained neurologists. Neurologic manifestations fell into 3 categories: central nervous system manifestations (dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and seizure), peripheral nervous system manifestations (taste impairment, smell impairment, vision impairment, and nerve pain), and skeletal muscular injury manifestations.

RESULTS Of 214 patients (mean [SD] age, 52.7 [15.5] years; 87 men [40.7%]) with COVID-19, 126 patients (58.9%) had nonsevere infection and 88 patients (41.1%) had severe infection according to their respiratory status. Overall, 78 patients (36.4%) had neurologic manifestations. Compared with patients with nonsevere infection, patients with severe infection were older, had more underlying disorders, especially hypertension, and showed fewer typical symptoms of COVID-19, such as fever and cough. Patients with more severe infection had neurologic manifestations, such as acute cerebrovascular diseases (5 [5.7%] vs 1 [0.8%]), impaired consciousness (13 [14.8%] vs 3 [2.4%]), and skeletal muscle injury (17 [19.3%] vs 6 [4.8%]).

CONCLUSIONS AND RELEVANCE Patients with COVID-19 commonly have neurologic manifestations. During the epidemic period of COVID-19, when seeing patients with neurologic manifestations, clinicians should suspect severe acute respiratory syndrome coronavirus 2 infection as a differential diagnosis to avoid delayed diagnosis or misdiagnosis and lose the chance to treat and prevent further transmission.

Editorial page 679

Supplemental content

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In December 2019, many unexplained pneumonia cases occurred in Wuhan, China, and rapidly spread to other parts of China, then to Europe, North America, and Asia. This outbreak was confirmed to be caused by a novel coronavirus (CoV).[1] The novel CoV was reported to have symptoms resembling that of severe acute respiratory syndrome CoV (SARS-CoV) in 2003.[2] Both shared the same receptor, angiotensin-converting enzyme 2 (ACE2).[3] Therefore, this virus was named SARS-CoV-2, and in February 2020, the World Health Organization (WHO) named the disease coronavirus disease 2019 (COVID-19). As of March 5, 2020, there were 95 333 confirmed cases of COVID-19 and 3282 deaths globally.[4]

Coronaviruses can cause multiple systemic infections or injuries in various animals.[5] The CoVs can adapt quickly and cross the species barrier, such as with SARS-CoV and Middle East respiratory syndrome CoV (MERS-CoV), causing epidemics or pandemics. Infection in humans often leads to severe clinical symptoms and high mortality.[6] As for COVID-19, several studies have described typical clinical manifestations including fever, cough, diarrhea, and fatigue. Coronavirus disease 2019 also has characteristic laboratory findings and lung computed tomography (CT) abnormalities.[7] However, to our knowledge, it has not been reported that patients with COVID-19 had any neurologic manifestations. Here, we report the characteristic neurologic manifestations of SARS-CoV-2 infection in 78 of 214 patients with laboratory-confirmed diagnosis of COVID-19 and treated at our hospitals, which are located in the epicenter of Wuhan.

Key Points

Question What are neurologic manifestations of patients with coronavirus disease 2019?

Findings In a case series of 214 patients with coronavirus disease 2019, neurologic symptoms were seen in 36.4% of patients and were more common in patients with severe infection (45.5%) according to their respiratory status, which included acute cerebrovascular events, impaired consciousness, and muscle injury.

Meaning Neurologic symptoms manifest in a notable proportion of patients with coronavirus disease 2019.

Methods

Study Design and Participants

This retrospective, observational study was done at 3 centers (Main District, West Branch, and Tumor Center) of Union Hospital of Huazhong University of Science and Technology (Wuhan, China). These 3 centers are designated hospitals assigned by the government to treat patients with COVID-19. We retrospectively analyzed consecutive patients from January 16, 2020, to February 19, 2020, who had been diagnosed as having COVID-19, according to WHO interim guidance.[8] A confirmed case of COVID-19 was defined as a positive result on high-throughput sequencing or real-time reverse-transcription polymerase chain reaction analysis of throat swab specimens. Throat swab samples were collected and placed into a collection tube containing preservation solution for the virus.[9] A SARS-CoV-2 infection was confirmed by real-time reverse-transcription polymerase chain reaction assay using a SARS-CoV-2 nucleic acid detection kit according to the manufacturer's protocol (Shanghai bio-germ Medical Technology Co). Radiologic assessments included chest and head CT, and all laboratory testing (a complete blood cell count, blood chemical analysis, coagulation testing, assessment of liver and renal function testing, C-reactive protein, creatine kinase, and lactate dehydrogenase) was performed according to the clinical care needs of the patient. Two hundred fourteen hospitalized patients with laboratory confirmation of SARS-CoV-2 were included in the analysis.[9] Before enrollment, verbal consent was obtained from patients or an accompanying relative for patients who could not give consent. The study was performed in accordance with the principles of the Declaration of Helsinki. This study was approved and written informed consent was waived by the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, on February 20, 2020, owing to the rapid emergence of the disease and the urgent need to collect data.

Data Collection

We reviewed electronic medical records, nursing records, laboratory findings, and radiologic examinations for all patients with laboratory-confirmed SARS-CoV-2 infection and collected data on age, sex, comorbidities (hypertension, diabetes, cardiac or cerebrovascular disease, malignancy, and chronic kidney disease), typical symptoms from onset to hospital admission (fever, cough, anorexia, diarrhea, throat pain, abdominal pain), nervous system symptoms, laboratory findings, and CT scan (chest and head if available). Subjective symptoms were provided by patients who were conscious, cognitively and mentally normal, and linguistically competent to respond to interview. Any missing or uncertain records were collected and clarified through direct communication with involved patients, health care clinicians, and their families. We defined the degree of severity of COVID-19 (severe vs nonsevere) at the time of admission using the American Thoracic Society guidelines for community-acquired pneumonia.[10]

All neurologic manifestations were reviewed and confirmed by 2 trained neurologists. Major disagreement between 2 reviewers was resolved by consultation with a third reviewer. Neurologic manifestations were categorized into 3 categories: central nervous system (CNS) manifestations (dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and seizure), peripheral nervous system (PNS) manifestations (taste impairment, smell impairment, vision impairment, and nerve pain), and skeletal muscular injury manifestations. Impaired consciousness includes the change of consciousness level (somnolence, stupor, and coma) and consciousness content (confusion and delirium). To avoid cross-infection during the outbreak, we had to minimize patients going out for examination. Therefore, the diagnosis of nervous system manifestations mainly depended on the subjective symptoms of patients and the examinations available.

Acute cerebrovascular disease includes ischemic stroke and cerebral hemorrhage diagnosed by clinical symptoms and head CT. Seizure is based on the clinical symptoms at the time of presentation. Skeletal muscle injury was defined as when a patient had skeletal muscle pain and elevated serum creatine kinase level greater than 200 U/L (to convert to microkatals per liter, multiply by 0.0167).[7]

Statistical Analysis

For baseline data, mean and standard deviations (SD) were used for normally distributed data and median and range for data that were not normally distributed. Categorical variables were expressed as counts and percentages. Continuous variables were compared by using the Wilcoxon rank sum test. Proportions for categorical variables were compared using the χ^2 test. All statistical analyses were performed using R, version 3.3.0, software (the R Foundation). The significance threshold was set at a 2-sided *P* value less than .05.

Results

Demographic and Clinical Characteristics

A total of 214 hospitalized patients with confirmed SARS-CoV-2 infection were included in the analysis. Their demographic and clinical characteristics were shown in **Table 1**. Their mean (SD) age was 52.7 (15.5) years, and 87 were men (40.7%). Of these patients, 83 (38.8%) had at least 1 of the following underlying disorders: hypertension (51 [23.8%]), diabetes (30 [14.0%]), cardiac or cerebrovascular disease (15 [7.0%]), and malignancy (13 [6.1%]). The most common symptoms at onset of illness were fever (132 [61.7%]), cough (107 [50.0%]), and anorexia (68 [31.8%]). Seventy-eight patients (36.4%) had nervous system manifestations: CNS (53 [24.8%]), PNS (19 [8.9%]), and skeletal muscle injury (23 [10.7%]). In patients with CNS manifestations, the most common reported symptoms were dizziness (36 [16.8%]) and headache (28 [13.1%]). In patients with PNS symptoms, the most common reported symptoms were taste impairment (12 [5.6%]) and smell impairment (11 [5.1%]).

According to the American Thoracic Society guidelines for community-acquired pneumonia,[10] 88 patients (41.1%) had severe infection and 126 patients (58.9%) had nonsevere infection. The patients with severe infection were significantly older (mean [SD] age, 58.2 [15.0] years vs 48.9 [14.7] years; $P < .001$) and more likely to have other underlying disorders (42 [47.7%] vs 41 [32.5%]; $P = .03$), especially hypertension (32 [36.4%] vs 19 [15.1%]; $P < .001$), and had fewer typical symptoms of COVID-19 such as fever (40 [45.5%] vs 92 [73%]; $P < .001$) and dry cough (30 [34.1%] vs 77 [61.1%]; $P < .001$). Moreover, nervous system manifestations were significantly more common in severe infections compared with nonsevere infections (40 [45.5%] vs 38 [30.2%], $P = .02$). They included acute cerebrovascular disease (5 [5.7%]; 4 patients with ischemic stroke and 1 with cerebral hemorrhage who died later of respiratory failure; vs 1 [0.8%]; 1 patient with ischemic stroke; $P = .03$, **Figure**), impaired consciousness (13 [14.8%] vs 3 [2.4%]; $P < .001$), and skeletal muscle injury (17 [19.3%] vs 6 [4.8%]; $P < .001$). In the severe group, 1 patient had a seizure characterized by a sudden onset of limb twitching, foaming in the mouth, and loss of consciousness, which lasted for 3 minutes.

Apart from cerebrovascular disease and impaired consciousness, most neurologic manifestations occurred early in the illness (median time, 1-2 days). Of 6 patients with acute cerebrovascular disease, 2 arrived at the emergency department owing to sudden onset of hemiplegia but without any typical symptoms (fever, cough, anorexia, and diarrhea) of COVID-19. Their lung lesions were found by an emergent lung CT and were diagnosed as having COVID-19 by a positive SARS-CoV-2 nucleic acid detection in the later stage. Some patients with fever and headache were admitted to the neurology ward after initially being ruled out of COVID-19 by routine blood test results and a screening lung CT in the clinic. However, several days later, they had typical COVID-19 symptoms such as cough, throat pain, lower lymphocyte count, and ground-glass opacity appearance on lung CT. Their diagnosis of COVID-19 was confirmed by a positive nucleic acid test and then they were transferred to the isolation ward.

Laboratory Findings in Patients and With Severe and Nonsevere Infection

Table 2 showed the laboratory findings in severe and nonsevere subgroups. Patients with severe infection had more increased inflammatory response, including higher white blood cell counts, neutrophil counts, lower lymphocyte counts, and increased C-reactive protein levels compared with those patients with nonsevere infection (white blood cell count: median, 5.4×10^9/L [range, 0.1-20.4] vs 4.5×10^9/L [range, 1.8-14.0]; $P < .001$; neutrophil: median, 3.8×10^9/L [range, 0.0-18.7] vs 2.6×10^9/L [range, 0.7-11.8]; $P < .001$; lymphocyte count: median, 0.9×10^9/L [range, 0.1-2.6] vs 1.3×10^9/L [range, 0.4-2.6]; $P < .001$; C-reactive protein: median, 37.1 mg/L [range, 0.1-212.0] vs 9.4 mg/L [range, 0.2-126.0]; $P < .001$). The patients with severe infection had higher D-dimer levels than patients with nonsevere infection (median, 0.9 mg/L [range, 0.1-20.0] vs 0.4 mg/L [range, 0.2-8.7]; $P < .001$), which was indicative of consumptive coagulation system. In addition, patients with severe infection had multiple organ involvement, such as serious liver (increased lactate dehydrogenase, alanine aminotransferase, and aspartate aminotransferase levels), kidney (increased blood urea nitrogen and creatinine levels), and skeletal muscle damage (increased creatinine kinase levels).

Laboratory Findings in Patients With and Without CNS Symptoms

Table 3 showed the laboratory findings of patients with and without CNS symptoms. We found that patients with CNS symptoms had lower lymphocyte levels, platelet counts, and higher blood urea nitrogen levels compared with those without CNS symptoms (lymphocyte count: median, 1.0×10^9/L [range, 0.1-2.3] vs 1.2×10^9/L [range, 0.2-2.6], $P = .049$; platelet count: median, 180.0×10^9/L [range, 18.0-564.0] vs 227.0×10^9/L [range, 42.0-583.0], $P = .005$; blood urea nitrogen: median, 4.5 mmol/L [range, 1.6-48.1] vs 4.1 mmol/L [range,

Table 1. Clinical Characteristics of Patients With COVID-19

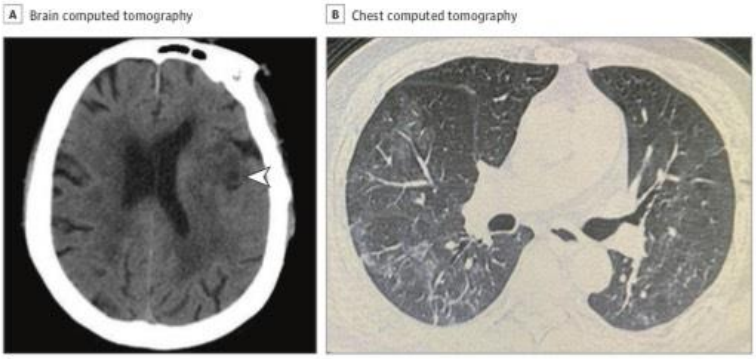
Characteristic	No. (%) Total (N = 214)	Severe (n = 88)	Nonsevere (n = 126)	P value[a]
Age, mean (SD), y	52.7 (15.5)	58.2 (15.0)	48.9 (14.7)	
Age, y				
<50	90 (42.1)	24 (27.3)	66 (52.4)	<.001
≥50	124 (57.9)	64 (72.7)	60 (47.6)	
Sex				
Female	127 (59.3)	44 (50.0)	83 (65.9)	.02
Male	87 (40.7)	44 (50.0)	43 (34.1)	
Comorbidities				
Any	83 (38.8)	42 (47.7)	41 (32.5)	.03
Hypertension	51 (23.8)	32 (36.4)	19 (15.1)	<.001
Diabetes	30 (14.0)	15 (17.0)	15 (11.9)	.29
Cardiac or cerebrovascular disease	15 (7.0)	7 (8.0)	8 (6.3)	.65
Malignancy	13 (6.1)	5 (5.7)	8 (6.3)	.84
Chronic kidney disease	6 (2.8)	2 (2.3)	4 (3.2)	.69
Typical symptoms				
Fever	132 (61.7)	40 (45.5)	92 (73.0)	<.001
Cough	107 (50.0)	30 (34.1)	77 (61.1)	<.001
Anorexia	68 (31.8)	21 (23.9)	47 (37.3)	.04
Diarrhea	41 (19.2)	13 (14.8)	28 (22.2)	.17
Throat pain	31 (14.5)	10 (11.4)	21 (16.7)	.28
Abdominal pain	10 (4.7)	6 (6.8)	4 (3.2)	.21
Nervous system symptoms				
Any	78 (36.4)	40 (45.5)	38 (30.2)	.02
CNS	53 (24.8)	27 (30.7)	26 (20.6)	.09
Dizziness	36 (16.8)	17 (19.3)	19 (15.1)	.42
Headache	28 (13.1)	15 (17.0)	13 (10.3)	.15
Impaired consciousness	16 (7.5)	13 (14.8)	3 (2.4)	<.001
Acute cerebrovascular disease	6 (2.8)	5 (5.7)	1 (0.8)	.03
Ataxia	1 (0.5)	1 (1.1)	0	NA
Seizure	1 (0.5)	1 (1.1)	0	NA
PNS	19 (8.9)	7 (8.0)	12 (9.5)	.69
Impairment				
Taste	12 (5.6)	3 (3.4)	9 (7.1)	.24
Smell	11 (5.1)	3 (3.4)	8 (6.3)	.34
Vision	3 (1.4)	2 (2.3)	1 (0.8)	.37
Nerve pain	5 (2.3)	4 (4.5)	1 (0.8)	.07
Skeletal muscle injury	23 (10.7)	17 (19.3)	6 (4.8)	<.001
Onset of symptoms to hospital admission, median (range), d				
CNS				
Dizziness	1 (1-30)	1 (1-30)	1 (1-14)	NA
Headache	1 (1-14)	1 (1-3)	3 (1-14)	NA
Impaired consciousness	8 (1-25)	10 (1-25)	1 (1-3)	NA
Acute cerebrovascular disease	9 (1-18)	10 (1-18)	1 (1)	NA
Ataxia	2 (2)	2 (2)	NA	NA
Seizure	2 (2)	2 (2)	NA	NA
PNS				
Impairment				
Taste	2 (1-5)	3 (1-3)	2 (1-5)	NA
Smell	2 (1-5)	1 (1-4)	2 (1-5)	NA
Vision	2 (1-3)	3 (2-3)	1 (1)	NA
Nerve pain	1 (1-1)	1 (1-1)	1 (1)	NA
Skeletal muscle injury	1 (1-11)	1 (1-11)	1 (1-6)	NA

Abbreviations: CNS, central nervous system; COVID-19, coronavirus disease 2019; NA, not applicable; PNS, peripheral nervous system.

[a] *P* values indicate differences between patients with severe and nonsevere infection, and *P* less than .05 was considered statistically significant.

1.5-19.1], $P = .04$). For the severe subgroup, patients with CNS symptoms also had lower lymphocyte levels and platelet counts and higher blood urea nitrogen levels compared with those without CNS symptoms (lymphocyte count: median, 0.7 $\times 10^9$/L [range, 0.1-1.6] vs 0.9 $\times 10^9$/L [range, 0.2-2.6], $P = .007$; platelet count: median, 169.0 $\times 10^9$/L [range, 18.0-564.0] vs

Figure. Representative Computed Tomography (CT) Images of a Patient With Coronavirus Disease 2019 With New Onset of Ischemic Stroke



A, Brain CT image 1 day after ischemic stroke. White arrowhead indicates the ischemic lesion. B, Chest CT image 1 day after ischemic stroke.

Table 2. Laboratory Findings of Patients With COVID-19

Laboratory finding	Median (range) Total (N = 214)	Severe (n = 88)	Nonsevere (n = 126)	*P* value[a]
Count, $\times 10^9$/L				
White blood cell	4.9 (0.1-20.4)	5.4 (0.1-20.4)	4.5 (1.8-14.0)	.008
Neutrophil	3.0 (0.0-18.7)	3.8 (0.0-18.7)	2.6 (0.7-11.8)	<.001
Lymphocyte	1.1 (0.1-2.6)	0.9 (0.1-2.6)	1.3 (0.4-2.6)	<.001
Platelet	209.0 (18.0-583.0)	204.5 (18.0-576.0)	219.0 (42.0-583.0)	.25
C-reactive protein, mg/L	12.2 (0.1-212.0)	37.1 (0.1-212.0)	9.4 (0.4-126.0)	<.001
D-dimer, mg/L	0.5 (0.1-20.0)	0.9 (0.1-20.0)	0.4 (0.2-8.7)	<.001
Creatine kinase, U/L	64.0 (8.8-12216.0)	83.0 (8.8-12216.0)	59.0 (19.0-1260.0)	.004
Lactate dehydrogenase, U/L	241.5 (2.2-908.0)	302.0 (2.2-880.0)	215.0 (2.5-908.0)	<.001
Aminotransferase, U/L				
Alanine	26.0 (5.0-1933.0)	32.5 (5.0-1933.0)	23.0 (6.0-261.0)	.04
Aspartate	26.0 (8.0-8191.0)	34.0 (8.0-8191.0)	23.0 (9.0-244.0)	<.001
Blood urea nitrogen, mmol/L	4.1 (1.5-48.1)	4.6 (1.5-48.1)	3.8 (1.6-13.7)	<.001
Creatinine, μmol/L	68.2 (35.9-9435.0)	71.6 (35.9-9435.0)	65.6 (39.4-229.1)	.03

Abbreviation: COVID-19, coronavirus disease 2019.

SI conversion factor: To convert aminotransferase levels to microkatals per liter, multiply by 0.0167; creatine kinase to microkatals per liter, multiply by 0.0167; lactate dehydrogenase to microkatals per liter, multiply by 0.0167.

[a] *P* values indicate differences between patients with severe and nonsevere infection, and *P* less than .05 was considered statistically significant.

220.0 × 10^9/L [range, 109.0-576.0], *P* = .04; blood urea nitrogen: median, 5.0 mmol/L [range, 2.3-48.1] vs 4.4 mmol/L [range, 1.5-19.1], *P* = .04). For the nonsevere subgroup, there were no significant differences in laboratory findings of patients with and without CNS symptoms.

Laboratory Findings in Patients With and Without PNS Symptoms

Table 4 showed the laboratory findings of patients with and without PNS symptoms. We found that there were no significant differences in laboratory findings of patients with PNS and those without PNS. Similar results were also found in the severe subgroup and nonsevere subgroup, respectively.

Laboratory Findings in Patients With and Without Skeletal Muscle Injury

The eTable in the Supplement shows the laboratory findings of patients with and without skeletal muscle injury. Compared with the patients without muscle injury, patients with muscle injury had significantly higher levels of creatine kinase (median, 400.0 U/L [range 203.0-12216.0] vs median, 58.5 U/L [range 8.8-212.0]; *P* < .001), regardless of their severity. Meanwhile, patients with muscle injury had higher neutrophil counts, lower lymphocyte counts, higher C-reactive protein levels, and higher D-dimer levels. The abnormalities were manifestations of increased inflammatory response and blood coagulation function. In addition, we found that patients with muscle injury had multiorgan damage, including more serious liver (increased lactate dehydrogenase, alanine aminotransferase, and aspartate aminotransferase levels) and kidney (increased blood urea nitrogen and creatinine levels) abnormalities.

For the severe group, patients with skeletal muscle injury had decreased lymphocyte counts and more serious liver injury (increased lactate dehydrogenase, alanine aminotransferase, and aspartate aminotransferase levels) and kidney injury (increased creatinine levels).

Table 3. Laboratory Findings of Patients With COVID-19 With CNS Symptoms[a]

Laboratory finding	Median (range)								
	Total			Severe			Nonsevere		
	With CNS symptoms (n = 53)	Without CNS symptoms (n = 161)	P value	With CNS symptoms (n = 27)	Without CNS symptoms (n = 61)	P value	With CNS symptoms (n = 26)	Without CNS symptoms (n = 100)	P value
Count, $\times 10^9$/L									
White blood cell	4.6 (0.1-12.5)	4.9 (1.8-20.4)	.58	5.3 (0.1-12.5)	5.5 (1.9-20.4)	.77	4.1 (2.4-11.0)	4.6 (1.8-14.0)	.40
Neutrophil	2.6 (0.0-10.9)	3.1 (0.7-18.7)	.41	3.8 (0.0-10.9)	3.6 (0.7-18.7)	>.99	2.2 (0.9-7.4)	2.8 (0.7-11.8)	.11
Lymphocyte	1.0 (0.1-2.3)	1.2 (0.2-2.6)	.049	0.7 (0.1-1.6)	0.9 (0.2-2.6)	.007	1.3 (0.7-2.3)	1.3 (0.4-2.6)	.49
Platelet	180.0 (18.0-564.0)	227.0 (42.0-583.0)	.005	169.0 (18.0-564.0)	220.0 (109.0-576.0)	.04	188.5 (110.0-548.0)	232.0 (42.0-583.0)	.09
C-reactive protein, mg/L	14.1 (0.1-212.0)	11.4 (0.1-204.5)	.31	48.6 (0.1-212.0)	26.1 (0.1-204.5)	.68	7.4 (3.1-111.0)	9.8 (0.4-126.0)	.82
D-dimer, mg/L	0.5 (0.2-9.7)	0.5 (0.1-20.0)	.75	1.2 (0.2-9.7)	0.9 (0.1-20.0)	.42	0.4 (0.2-6.4)	0.4 (0.2-8.7)	.46
Creatine kinase, U/L	79.0 (8.8-12216.0)	60.5 (19.0-1260.0)	.17	104.0 (8.8-12 216.0)	64.0 (19.0-1214.0)	.08	52.5 (28.0-206.0)	59.0 (19.0-1260.0)	.56
Lactate dehydrogenase, U/L	243.0 (2.2-880.0)	241.0 (3.5-908.0)	.77	334.0 (2.2-880.0)	299.0 (3.5-743.0)	.32	198.0 (2.5-417.0)	226.0 (121.0-908.0)	.14
Aminotransferase, U/L									
Alanine	27.0 (5.0-261.0)	26.0 (6.0-1933.0)	.21	35.0 (5.0-259.0)	31.0 (7.0-1933.0)	.32	25.5 (13.0-261.0)	23.0 (6.0-135.0)	.68
Aspartate	29.5 (13.0-213.0)	26.0 (8.0-8191.0)	.10	35.5 (14.0-213.0)	34.0 (8.0-8191.0)	.32	23.0 (13.0-198.0)	23.5 (9.0-244.0)	.56
Blood urea nitrogen, mmol/L	4.5 (1.6-48.1)	4.1 (1.5-19.1)	.04	5.0 (2.3-48.1)	4.4 (1.5-19.1)	.04	3.9 (1.6-9.4)	3.8 (1.7-13.7)	.57
Creatinine, μmol/L	71.7 (37.1-1299.2)	66.3 (35.9-9435.0)	.06	71.7 (37.1-1299.2)	68.4 (35.9-9435.0)	.25	72.0 (40.3-133.6)	63.4 (39.4-229.1)	.27

Abbreviations: CNS, central nervous system; COVID-19, coronavirus disease 2019.

SI conversion factor: To convert aminotransferase levels to microkatals per liter, multiply by 0.0167; creatine kinase to microkatals per liter, multiply by 0.0167; lactate dehydrogenase to microkatals per liter, multiply by 0.0167.

[a] *P* values indicate differences between patients with and without CNS symptoms, and *P* less than .05 was considered statistically significant.

Discussion

To our knowledge, this is the first report on detailed neurologic manifestations of the hospitalized patients with COVID-19. As of February 19, 2020, of 214 patients included in this study, 88 (41.1%) had severe infection and 126 (58.9%) had nonsevere infection. Of these, 78 (36.4%) had various neurologic manifestations that involved CNS, PNS, and skeletal muscles. Compared with patients with nonsevere infection, patients with severe infection were older and had more hypertension but fewer typical symptoms such as fever and cough. Patients with severe infection were more likely to develop neurologic manifestations, especially acute cerebrovascular disease, conscious disturbance, and skeletal muscle injury. Most neurologic manifestations occurred early in the illness (the median time to hospital admission was 1-2 days). Some patients without typical symptoms (fever, cough, anorexia, and diarrhea) of COVID-19 came to the hospital with only neurologic manifestation as their presenting symptoms. Therefore, for patients with COVID-19, we need to pay close attention to their neurologic manifestations, especially for those with severe infections, which may have contributed to their death. Moreover, during the epidemic period of COVID-19, when seeing patients with these neurologic manifestations, physicians should consider SARS-CoV-2 infection as a differential diagnosis to avoid delayed diagnosis or misdiagnosis and prevention of transmission.

In January 2020,[3] ACE2 was identified as the functional receptor for SARS-CoV-2, which is present in multiple human organs, including nervous system and skeletal muscles.[11] The expression and distribution of ACE2 remind us that the SARS-CoV-2 may cause some neurologic manifestations through direct or indirect mechanisms. Autopsy results of patients with COVID-19 showed that the brain tissue was hyperemic and edematous and some neurons degenerated.[12] Neurologic injury has been confirmed in the infection of other CoVs such as in SARS-CoV and MERS-CoV. The researchers detected SARS-CoV nucleic acid in the cerebrospinal fluid of those patients and also in their brain tissue on autopsy.[13,14]

Central nervous system symptoms were the main form of neurologic injury in patients with COVID-19 in this study. The pathologic mechanism may be from the CNS invasion of SARS-CoV-2, similar to SARS and MERS viruses. As with other respiratory viruses, SARS-COV-2 may enter the CNS through the hematogenous or retrograde neuronal route. The latter can be supported by the fact that some patients in this study had smell impairment. We also found that the lymphocyte counts were lower for patients with CNS symptoms than without CNS symptoms. This phenomenon may be indicative of the immunosuppression in patients with COVID-19 with CNS symptoms, especially in the severe subgroup. Moreover, we found

Table 4. Laboratory Findings of Patients With COVID-19 With PNS Symptoms

Laboratory finding	Median (range)								
	Total			Severe			Nonsevere		
	With PNS symptoms (n = 19)	Without PNS symptoms (n = 195)	*P* value	With PNS symptoms (n = 7)	Without PNS symptoms (n = 81)	*P* value	With PNS symptoms (n = 12)	Without PNS symptoms (n = 114)	*P* value
Count, $\times 10^9$/L									
White blood cell	4.8 (2.8-7.5)	4.9 (0.1-20.4)	.74	4.5 (3.1-6.8)	5.6 (0.1-20.4)	.11	4.9 (2.8-7.5)	4.4 (1.8-14.0)	.27
Neutrophil	2.8 (1.5-5.4)	3.0 (0.0-18.7)	.74	2.6 (1.5-5.3)	4.1 (0.0-18.7)	.10	2.9 (1.9-5.4)	2.5 (0.7-11.8)	.21
Lymphocyte	1.2 (0.6-2.6)	1.1 (0.1-2.6)	.43	1.2 (0.6-1.6)	0.9 (0.1-2.6)	.26	1.2 (0.7-2.6)	1.3 (0.4-2.4)	.92
Platelet	204.0 (111.0-305.0)	213.0 (18.0-583.0)	.56	204.0 (111.0-245.0)	205.0 (18.0-576.0)	.56	214.5 (155.0-305.0)	219.0 (42.0-583.0)	.81
C-reactive protein, mg/L	12.0 (3.1-81.0)	12.3 (0.1-212.0)	.45	7.5 (3.1-76.4)	43.7 (0.1-212.0)	.13	13.0 (3.1-81.0)	8.8 (0.4-126.0)	.60
D-dimer, mg/L	0.4 (0.2-9.5)	0.5 (0.1-20.0)	.40	0.5 (0.2-9.5)	1.3 (0.1-20.0)	.27	0.4 (0.2-4.5)	0.4 (0.2-8.7)	.99
Creatine kinase, U/L	67.0 (32.0-1214.0)	64.0 (8.8-12216.0)	.41	105.0 (32.0-1214.0)	83.0 (8.8-12216.0)	.76	66.0 (42.0-171.0)	57.5 (19.0-1260.0)	.29
Lactate dehydrogenase, U/L	205.0 (2.5-517.0)	242.0 (2.2-908.0)	.28	170.0 (46.0-517.0)	309.0 (2.2-880.0)	.05	254.0 (2.5-481.0)	215.0 (2.9-908.0)	.67
Aminotransferase, U/L									
Alanine	26.0 (5.0-116.0)	27.0 (6.0-1933.0)	.70	19.0 (5.0-80.0)	35.0 (8.0-1933.0)	.23	26.0 (8.0-116.0)	23.0 (6.0-261.0)	.56
Aspartate	22.0 (8.0-115.0)	27.0 (9.0-8191.0)	.29	22.0 (8.0-53.0)	35.5 (12.0-8191.0)	.13	22.0 (14.0-115.0)	23.5 (9.0-244.0)	>.99
Blood urea nitrogen, mmol/L	4.1 (1.6-8.8)	4.1 (1.5-48.1)	.76	4.2 (3.5-8.8)	4.7 (1.5-48.1)	.96	3.7 (1.6-5.3)	3.9 (1.7-13.7)	.66
Creatinine, μmol/L	62.5 (48.1-121.4)	68.3 (35.9-9435.0)	.46	71.4 (58.3-121.4)	71.7 (35.9-9435.0)	.72	59.9 (48.1-77.3)	66.6 (39.4-229.1)	.24

Abbreviations: COVID-19, coronavirus disease 2019; PNS, peripheral nervous system.

SI conversion factor: To convert aminotransferase levels to microkatals per liter, multiply by 0.0167; creatine kinase to microkatals per liter, multiply by 0.0167; lactate dehydrogenase to microkatals per liter, multiply by 0.0167.

[a] *P* values indicate differences between patients with and without PNS symptoms, and *P* less than .05 was considered statistically significant.

patients with severe infection had higher D-dimer levels than that of patients with nonsevere infection. This may be the reason why patients with severe infection are more likely to develop cerebrovascular disease.

Consistent with the previous studies,[7] muscle symptoms were also common in our study. We speculate that the symptom was owing to skeletal muscle injury, as confirmed by elevated creatine kinase levels. We found that patients with muscle symptoms had higher creatine kinase and lactate dehydrogenase levels than those without muscle symptoms. Furthermore, creatine kinase and lactate dehydrogenase levels in patients with severe infection were much higher than those of patients with nonsevere infection. This injury could be associated with ACE2 in skeletal muscle.[15] However, SARS-CoV, using the same receptor, was not detected in skeletal muscle by postmortem examination.[16] Therefore, whether SARS-CoV-2 infects skeletal muscle cells by binding with ACE2 needs to be further studied. One other reason was the infection-mediated harmful immune response that caused the nervous system abnormalities. Significantly elevated proinflammatory cytokines in serum may cause skeletal muscle damage.

Limitations

This study has several limitations. First, only 214 patients were studied, which could cause biases in clinical observation. It would be better to include more patients from Wuhan, other cities in China, and even other countries. Second, all data were abstracted from the electronic medical records; certain patients with neurologic symptoms might not be captured if their neurologic manifestations were too mild, such as with taste impairment and smell impairment. Third, because most patients were still hospitalized and information regarding clinical outcomes was unavailable at the time of analysis, it was difficult to assess the effect of these neurologic manifestations on their outcome, and continued observations of the natural history of disease are needed. Fourth, during the outbreak period of COVID-19, because of the influx of many patients infected with SARS-CoV-2, advanced neuroimaging, such as magnetic resonance imaging and diagnostic procedures such as lumbar puncture and electromyography/nerve conduction velocity, was purposefully avoided to reduce the risk of cross infection. Therefore, in our study, most of the symptoms were a patient's subjective descriptions. We could not distinguish whether these neurologic manifestations are caused by the virus directly or by the pulmonary disease or other organ damage indirectly.

Conclusions

In conclusion, SARS-CoV-2 may infect nervous system and skeletal muscle as well as the respiratory tract. In those with

severe infection, neurologic involvement is greater, which includes acute cerebrovascular diseases, impaired consciousness, and skeletal muscle injury. Their clinical conditions may worsen, and patients may die sooner. This study may offer important new clinical information on COVID-19 that would help clinicians raise awareness of its involvement of neurologic manifestations. It is especially meaningful to learn that for those with severe COVID-19, rapid clinical deterioration or worsening could be associated with a neurologic event such as stroke, which would contribute to its high mortality rate. Moreover, during the epidemic period of COVID-19, when seeing patients with these neurologic manifestations, clinicians should consider SARS-CoV-2 infection as a differential diagnosis to avoid delayed diagnosis or misdiagnosis and prevention of transmission.

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Original article

New-onset anosmia and ageusia in adult patients diagnosed with SARS-CoV-2 infection

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ABSTRACT

Objectives: We investigated the prevalence of anosmia and ageusia in adult patients with a laboratory-confirmed diagnosis of infection with severe acute respiratory distress syndrome coronavirus-2 (SARS-CoV-2).

Methods: This was a retrospective observational analysis of patients infected with SARS-CoV-2 admitted to hospital or managed in the community and their household contacts across a London population during the period March 1st to April 1st, 2020. Symptomatology and duration were extracted from routinely collected clinical data and follow-up telephone consultations. Descriptive statistics were used.

Results: Of 386 patients, 141 (92 community patients, 49 discharged inpatients) were included for analysis; 77/141 (55%) reported anosmia and ageusia, nine reported only ageusia and three only anosmia. The median onset of anosmia in relation to onset of SARS-CoV-2 disease (COVID-19) symptoms (as defined by the Public Health England case definition) was 4 days (interquartile range (IQR) 5). Median duration of anosmia was 8 days (IQR 16). Median duration of COVID-19 symptoms in community patients was 10 days (IQR 8) versus 18 days (IQR 13.5) in admitted patients. As of April 1, 45 patients had ongoing COVID-19 symptoms and/or anosmia; 107/141 (76%) patients had household contacts, and of 185 non-tested household contacts 79 (43%) had COVID-19 symptoms with 46/79 (58%) reporting anosmia. Six household contacts had anosmia only.

Conclusions: Over half of the positive patients reported anosmia and ageusia, suggesting that these should be added to the case definition and used to guide self-isolation protocols. This adaptation may be integral to case findings in the absence of population-level testing. Until we have successful population-level vaccination coverage, these steps remain critical in the current and future waves of this pandemic.
A. Patel, Clin Microbiol Infect 2020;26:1236

Introduction

Since the outbreak of the severe acute respiratory syndrome coronavirus (SARS-CoV-2) pandemic—reported first from Wuhan, China in December 2019—there have been increasing reports of anosmia (total or partial loss of smell) and ageusia (total or partial loss of taste) amongst patients presenting with suspected or confirmed infection [1]. Early reports from Italy and South Korea showed anosmia in up to 34% of patients [2–4]. A more recent cross-European analysis looking at patients with mild to moderate SARS-CoV-2 disease (COVID-19) put this number at 85.6% [5].

Anosmia can occur in a wide range of viral infections; published literature estimates the prevalence of olfactory disorders, including anosmia, to be 11–40% [1,6–8]. The higher estimates (20–40%) were generated using data from patients in specialized smell and

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taste centres, and the lower estimate (11%) was based on data from general ear, nose, and throat clinics [8]. SARS-CoV-2 does not generate clinically significant nasal congestion or rhinorrhoea that would typically be associated with anosmia in other upper respiratory tract infections, and it has also been observed that anosmia manifests either early in the disease process or in patients with mild symptoms [1]. Early analysis of the 'Anosmia Reporting Tool' by the American Academy of Otolaryngology showed anosmia in 73% of patients prior to COVID-19 diagnosis, and was the initial symptom in 26.6%, suggesting that anosmia may be a presenting symptom of COVID-19 [9]. In the absence of a widespread population testing strategy, understanding the symptomatology of this new illness is critical to ensuring that the correct advice is given to patients and the public in relation to self-isolation leading to reduced population transmission.

In the United Kingdom (UK), the transmission of SARS-CoV-2 was first confirmed in February 2020. From March 1, SARS-CoV-2 was reported across England, Wales, Scotland and Ireland, indicating widespread community transmission. Public Health England guidance currently recognizes symptoms of COVID-19 to include fever $\geq$37.8°C and at least one of the symptoms persistent cough (with or without sputum), hoarseness, nasal discharge or congestion, shortness of breath, sore throat, wheezing or sneezing [10]. To date, anosmia and ageusia are not recognised symptoms in the disease case definition. However, there is increasing evidence of these symptoms presenting in patients who are otherwise asymptomatic, highlighting the possibility that new-onset anosmia and/or ageusia may be useful as a component of screening for the virus [4]. This is critical at this stage in the pandemic, as adding olfactory symptoms to the case definition of COVID-19 would be especially useful should anosmia and/or ageusia be shown to present early and in otherwise asymptomatic patients who may go on to require hospital admission.

In this retrospective analysis of both community and secondary-care patients in a London population diagnosed with SARS-CoV-2 infection, we aimed to establish the prevalence of new-onset anosmia and ageusia and place them within disease symptom progression. We also investigated whether the olfactory symptoms experienced by COVID-19 patients are accompanied by other nasal symptoms (congestion or rhinorrhoea) as with other post-viral olfactory disorders. Additionally, we investigated the presence of COVID-19 symptoms, anosmia and ageusia in the household contacts of these patients.

Methods

Ethics approval and consent to participate

Data were collected as part of routine care by the responsible clinical team. No patient-identifiable data are reported in this analysis. The need for written informed consent was waived by the Research Governance Office of Chelsea and Westminster NHS Foundation Trust.

Study design and participants

This was a retrospective, observational analysis of patients diagnosed either as inpatients at a 430-bed London acute teaching hospital or in the surrounding community. As well as receiving unwell patients warranting admission, the hospital adopted a community testing strategy to identify suspected COVID-19 cases. Unwell patients were screened through call centres and general practitioners, who referred patients suspected of having COVID-19 to a centralized response team. Depending on mobility, these patients were either directed to drive through SARS-CoV-2 testing clinics or visited at home by community testing teams. Patients were also assessed through a bespoke section of the emergency department. This community testing ceased on March 13th, 2020.

Nasopharyngeal and oral swabs were taken from all patients (both community and secondary care) and tested at a central reference laboratory using real-time reverse transcriptase polymerase chain reaction (PCR) (initially using a proprietary assay run by Public Health England, then from March 6th, 2020 onwards a commercial assay from AusDiagnostics®, Australia) for SARS-CoV-2. Patients who were considered to be clinically stable were allowed to self-isolate at home. Community patients were informed of their result by telephone. Inpatients had their symptoms and clinical course documented in their electronic healthcare record (Millennium: Cerner Corporation, Kansas City, Missouri, USA) by the admitting clinical team. Demographic and clinical data were collected from electronic health records for all patients included in the analysis. Details of onset of COVID-19 symptoms, anosmia and/or ageusia were extracted where present.

All patients with a laboratory diagnosis of COVID-19 between March 1 and April 1, 2020 were identified. Patients were included if they (a) had a positive diagnosis for COVID-19 based on real-time PCR detection of SARS-CoV-2, and (b) were tested in the community OR admitted to and discharged from hospital. Patients were excluded if they (a) died post-diagnosis, (b) were <16 years of age, (c) did not have an accurate record of symptom history (e.g. due to confusion or lack of memory), or (d) were readmitted to hospital or transferred to another healthcare facility. We excluded current inpatients because a large proportion had current oxygen requirements either through nasal cannulae or via face-masks. These devices could influence the assessment of anosmia. Additionally, these patients were in isolation wards with only essential care being given to limit onward transmission, which made them inaccessible for the purposes of this study.

Between April 13th and April 17th, 2020, telephone consultations were conducted with all identified patients to verify symptomatology and timeline to resolution of clinical symptoms. All patients were asked a series of standardized questions on the presence of COVID-19 symptoms and also diarrhoea, vomiting, myalgia, and any change in their sense of smell and taste. If changes in smell and/or taste were reported, further standardized questions were asked regarding time of onset relative to onset of COVID-19 symptoms, duration of change, and whether these symptoms had resolved. Only complete recovery from anosmia was considered as resolution of the symptom. Partial recovery was considered as hyposmia. At the time of this study there was little evidence associating anosmia and COVID-19, therefore the primary outcome was new-onset anosmia and the questionnaire was not scored [11]. Details of the presence of household contacts and their symptomatology were also routinely collected in line with public health guidance. Specifically, patients were asked whether household contacts had experienced COVID-19 symptoms and whether any of them had experienced anosmia.

Study outcome measures

The primary outcome measure was the prevalence of new-onset anosmia and/or associated ageusia. Secondary outcome measures included analysis of duration of COVID-19 symptoms (as outlined by the current Public Health England case definition) [10] and new-onset anosmia and/or associated ageusia. Clinical presentation was defined as mild versus severe depending on whether patients were admitted to hospital or isolated in the community. An additional outcome measure was the prevalence of new-onset anosmia amongst household contacts.

Results

Between March 1st and April 1st 2020, 386 patients were diagnosed as SARS-CoV-2-positive using real-time PCR detection (Fig. 1). Of these, 167 were excluded as they did not fit the study inclusion criteria. Of the remaining 219, 74 were not contactable for the follow-up telephone consultations after three attempts across multiple dates. The final analysis included 141 patients. Of these, 92 were treated in the community and 49 were admitted to and discharged from hospital.

Table 1 summarizes the most commonly reported COVID-19 symptoms. Of the 141 patients, 77 (55%) reported anosmia and ageusia. Three patients reported only anosmia. Nine patients reported only ageusia. No patients reported pre-existing anosmia. Nasal congestion was reported in 39/80 patients (49%) with anosmia and 43/89 patients (48%) with ageusia. Nasal symptoms in the absence of anosmia and/or ageusia were reported in 16/52 patients (31%).

Table 2 shows the median duration of COVID-19 symptoms and anosmia (duration of symptoms was not normally distributed). The data in the table exclude 14 patients who were clear about the presence of both COVID-19 symptoms and anosmia but were unable to give an accurate duration of the anosmia. Fig. 2 charts the onset and duration of anosmia in relation to onset of COVID-19 symptoms. The onset of anosmia ranged between 1 and 21 days, and the duration was reported to be between 1 and 30 days with 32/81 patients experiencing ongoing anosmia or hyposmia at the end of the study period.

Of the 141 patients, 107 (76%) had one or more household contacts (total number of household contacts = 195) during their isolation period. Five households contained two study participants each ($n = 10$), leaving 185 non-tested household contacts. Of these, 79 (43%) had COVID-19 symptoms and 46 (58%) had anosmia. Six household contacts had anosmia in the absence of other symptoms (Fig. 3).

Table 1
Patient demographics and frequency of COVID-19 symptoms in patients from a London community and secondary-care population between March 1st and April 1st, 2020

	Total	Community	Admitted
n	141	92 (65.2%)	49 (34.8%)
Mean age (range)	45.6 (20–93)	40.7 (20–87)	54.9 (22–93)
Sex (male/female)	83/58	58/34	27/22
Most common reported symptoms			
Fever	111 (75.7%)	70 (76.1%)	41 (83.7%)
Cough	102 (72.3%)	68 (73.9%)	34 (69.4%)
Myalgia	93 (66.0%)	67 (72.8%)	26 (53.1%)
Ageusia	89 (63.1%)	57 (62.0%)	32 (65.3%)
Shortness of breath	86 (61.0%)	54 (58.7%)	32 (65.3%)
Anosmia	80 (56.7%)	56 (60.9%)	24 (49.0%)
Nasal congestion	60 (42.6%)	43 (46.7%)	17 (34.7%)
Diarrhoea	45 (31.9%)	23 (25.0%)	22 (44.9%)
Vomiting	19 (13.5%)	11 (12.0%)	8 (16.3%)

Discussion

This analysis reports that over half of patients with COVID-19 experienced anosmia and/or ageusia. These findings are important as they support the increasing evidence associating anosmia and ageusia with SARS-CoV-2. They also represent a snapshot of the community setting at the early stages of the spread of this

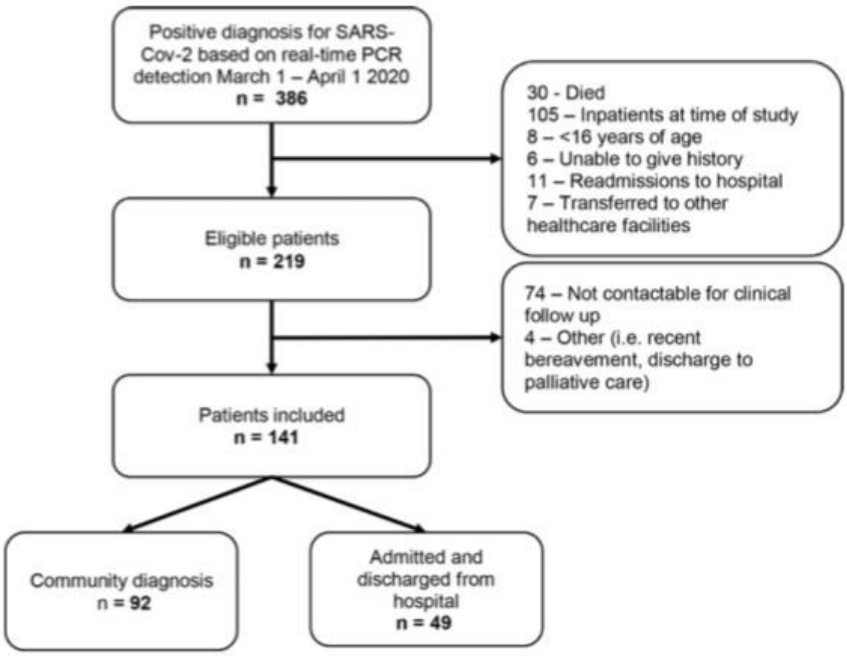

Fig. 1. Flow diagram of participant selection for patients positive for severe acute respiratory distress syndrome coronavirus-2 (SARS-CoV-2) from a London community and a secondary-care population between March 1st and April 1st, 2020.

Table 2
Natural history of COVID-19 symptoms and anosmia in patients from a London community and secondary-care population between March 1st and April 1st, 2020

	Total	Community	Admitted
Patients with resolved COVID-19 symptoms	114	83	31
Patients with unresolved COVID-19 symptoms	13	6	7
Median duration of COVID-19 symptoms in days (interquartile range)	12 (11.5)	10 (8)	118 (13.5)
Patients with resolved anosmia	49	34	15
Patients with unresolved anosmia/ongoing hyposmia	32	21	11
Median lag for onset of anosmia in days (IQR)	4 (5)	3 (3)	5 (4)
Median duration of anosmia in days (IQR)	8 (16)	14 (16)	7 (8.5)

IQR, interquartile range.

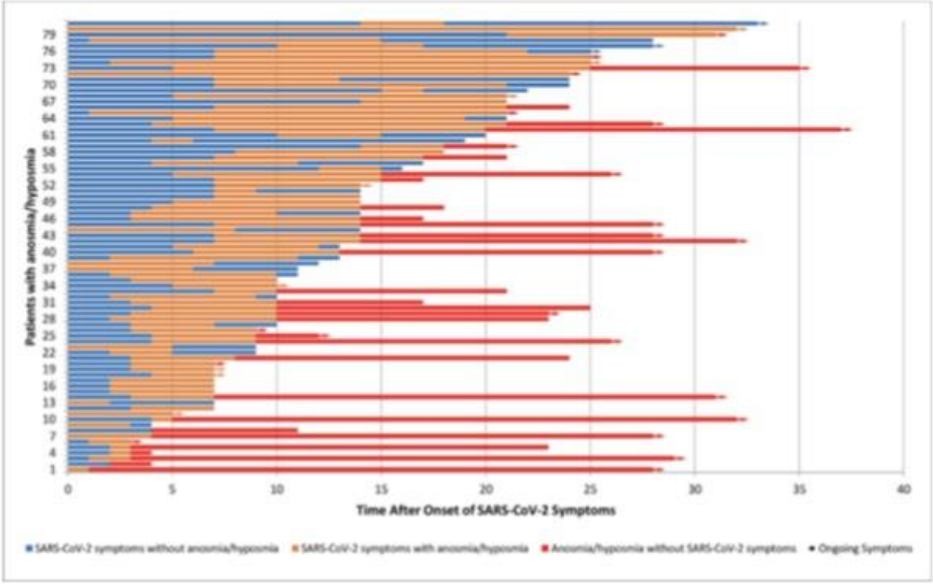

Fig. 2. Onset and duration (in days) of anosmia in relation to COVID-19 symptoms in patients from a London community and a secondary-care population between March 1st and April 1st, 2020. Arrow indicates ongoing symptoms at the time of telephone consultations.

pandemic in the UK, which is valuable given the early cessation of community testing.

The prevalence of anosmia in post-viral respiratory tract infections seen in specialist clinics is greater than in general ear nose and throat clinics [8]. This suggests that the pickup rates in specialist clinics are higher. Our analysis, though more comparable to that of a general clinic setting, found the prevalence of anosmia to be greater than that found in specialist anosmia clinics. This higher prevalence of anosmia in COVID-19 is broadly in line with the current literature, where anosmia has been identified as one of the most predictive symptoms of COVID-19 [12]. Of all patients with anosmia, the majority (52%) did not report concurrent nasal congestion. This supports data from a large cross-European analysis that showed olfactory disorders are prevalent in COVID-19 patients, who may not have nasal symptoms [5].

Patients who reported ageusia only could not accurately differentiate between losing their sense of taste or their sense of smell. This may be due to retronasal olfactory function being labelled as taste [13]. The gustatory system (transmitted via the glossopharyngeal, facial and vagal nerves) only recognizes the basic tastes (sweet, sour, salty, bitter and umami), but most of the culinary experiences are recognized by the olfactory nerve [14]. Indeed, there is a close association between anosmia and ageusia, which may make it difficult for patients to differentiate between the two [15]. In our analysis we therefore made the assumption that ageusia was unlikely to be present in the absence of anosmia, and we therefore considered these patients to have anosmia also.

In this study a sizeable proportion of patients reported anosmia and ageusia extending beyond the resolution of COVID-19 symptoms. Additionally, three patients reported anosmia in the absence of any other symptoms. Mild community-treated patients were more likely to report anosmia than those admitted to hospital, which supports emerging evidence associating new-onset anosmia with mild or absent COVID-19 symptoms [1,5]. Prospective studies are needed to investigate the epidemiological significance of this in the context of potential spread of disease by individuals with mild atypical presentations.

The relative short time span of onset of anosmia in relation to other COVID-19 symptoms suggests that anosmia may be a useful early diagnostic factor in this viral disease and may subsequently have a role in guiding isolation practice. Duration and time of onset of anosmia were twice as long in the hospital group, although this analysis was not powered to investigate the significance of the variation in findings between hospitalized and community

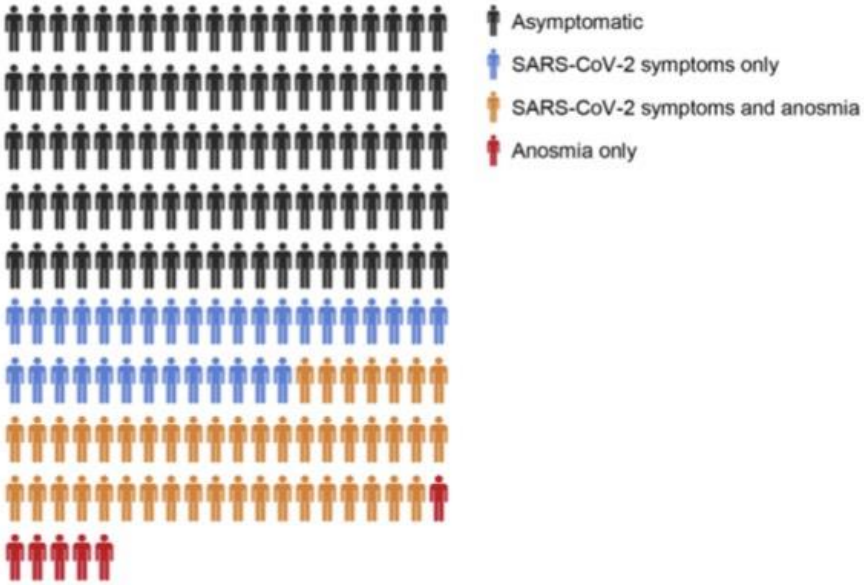

Fig. 3. The presence of COVID-19 symptoms and anosmia in non-tested household contacts ($n = 185$) of patients from a London community and a secondary-care population tested positive for severe acute respiratory distress syndrome coronavirus-2 (SARS-CoV-2) between March 1st and April 1st, 2020.

patients. Severe symptoms in hospitalized patients may initially overshadow the presence of anosmia, possibly explaining the delay in perceived onset. It is worth mentioning that, as of April 17th (end of the data collection period), 45 patients had ongoing COVID-19 symptoms and/or anosmia/hyposmia. This means the reported duration times are likely to be underrepresented.

All patients in this study were tested for SARS-CoV-2 due to clinical suspicion based on symptomatology. Therefore, by the nature of the selection process, it is unlikely that any COVID-19 patients with anosmia alone would have been tested. Over half of the symptomatic (but not tested) household contacts, however, reported anosmia, with a further six experiencing anosmia alone. Being close contacts of confirmed COVID-19 patients, it is likely the high prevalence of anosmia in this group is related to transmission of SARS-CoV-2. This shows consistency in prevalence of anosmia in an exposed (but not confirmed) population, but also that mild versions of the illness may present with anosmia alone. To obtain a true understanding of the clinical significance of anosmia in SARS-CoV-2, we need to prospectively investigate new-onset anosmia in the general population, potentially coupled with serological testing.

The strength of this study is that it provides an early insight into the chronological sequence of anosmia in COVID-19 and also the association between symptoms and household transmission. Since this analysis provides a snapshot of symptomatology in SARS-CoV-2-positive patients, it is not possible to draw population-wide conclusions. Recall bias of patients may also have influenced the clinically recorded data, especially of those hospitalized. Similarly, the absence of objective testing meant we were not able to clinically define the extent and severity of the anosmia and ageusia. Furthermore, physical examination was not possible in the community due to social distancing rules and the potential for onwards transmission. The use of a structured questionnaire, however, helped to ameliorate this possible reporting bias (Supplementary Material). It was not possible to estimate the number of asymptomatic COVID-19 patients in our community population as asymptomatic patients may have been less likely to present to hospital, and may not have been eligible for community testing as per PHE diagnostic criteria. Several patients had ongoing anosmia, and further follow-up will be required to further discern the duration of these symptoms.

This analysis did not include patients under the age of 16, and it has been widely reported that children do not appear to present in the same way as adults but may still be asymptomatic. The symptomatology of COVID-19 in children needs to be examined.

More than half the patients with confirmed COVID-19 suffered anosmia and ageusia. This is significant when compared with the prevalence of anosmia and ageusia in other post-viral upper respiratory tract infections. These findings suggest that anosmia and ageusia be added to existing case definitions for COVID-19 and used to guide self-isolation procedures. This is critical in the absence of population-level testing.

The findings of this research highlight the need to investigate new-onset anosmia in the general population, particularly in those without other symptoms. A better understanding of the long-term outcomes of anosmia in COVID-19 patients is needed. Until a time when we have successful population-level vaccination coverage, these steps remain critical to managing the current and subsequent waves of this pandemic.

Author contributions

AP and EC developed the study design. AP, EC, DA, and AA were responsible for data collection. AP, EC and AA assisted with data interpretation. AP and EC performed the literature search and wrote the first draft of the paper. All authors have critically read and commented on draft versions of the manuscript and approved the final version.

Transparency declaration

All authors have completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and declare the following. EC has received speaker fees from bioMerieux (2019). NM has received speaker fees from Beyer (2016) and Pfizer (2019) and received educational support from Eumedica (2016) and Baxter (2017). LSPM has consulted for bioMerieux (2013), DNAelectronics (2015–18), Dairy Crest (2017–2018), Umovis Lab (2020), received speaker fees from Profile Pharma (2018–2019) and Pfizer (2018–2020), received research grants from the National Institute for Health Research (2013–2020), CW+ Charity (2018–2019), and Leo Pharma (2016), and received educational support from Eumedica (2016–2018). AP, DLA, and AA have no conflicts of interest to declare. This research did not receive any grant from funding agencies in the public or commercial sectors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2020.05.026.

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