

Olfactory and Gustatory Dysfunctions in COVID-19 Patients: From a Different Perspective

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Purpose: The prevalence of sensory disorders (smell and/or taste) in affected patients has shown a high variability of 5% to 98% during the COVID-19 outbreak, depending on the methodology, country, and study. Loss of smell and taste occurring in COVID-19 cases are now recognized by the international scientific community as being among the main symptoms of the disease. This study investigates loss of smell and taste in outpatients and hospitalized patients with laboratory-confirmed COVID-19 infection.

Methods: Enrolled in the study were patients with a positive PCR test for COVID-19. Excluded were patients with chronic rhinosinusitis, nasal polyposis, common cold, influenza, and olfactory/gustatory dysfunction predating the pandemic. Patients were asked about changes in their sense of smell and taste by structured questionnaire. Their status was classified according to severity of the symptoms.

Results: A total of 217 patients were included in the study, of whom 129 received outpatient treatment, whereas 88 were hospitalized; mean age was 41.74 years (range 18–76), 59.4% were male. At evaluation for olfactory dysfunction, 53.9% of the patients were found to be normal, whereas 33.2% were anosmic. No gustatory dysfunction was found in 49.8% of patients, whereas in those with loss of taste, the most commonly recorded symptom was ageusia. Anosmia was significantly more common in outpatients ($P = 0.038$). Presentation of chemosensorial symptoms in women was higher than in men ($P = 0.009$). No correlation was found between olfactory and gustatory dysfunction and age ($P = 0.178$).

Conclusions: About one-half of our patients presented olfactory and/or gustatory deficits, and loss of smell was more common in mild cases. It should be considered; a sudden, severe, and isolated loss of smell and/or taste may also be present in COVID-19 patients who are otherwise asymptomatic. We suggest that identification of persons with these signs and early isolation could prevent spread of the disease in the community.

Key Words: Ageusia, anosmia, COVID-19, gustatory, hospitalization, olfactory, SARS-CoV-2

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Coronavirus disease 2019 (COVID-19) caused by the Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2), emerged in December 2019 in the Chinese city of Wuhan and spread worldwide, causing a pandemic.¹ The US Centers for Disease Control list new loss of smell or taste among the main symptoms of COVID-19.²

A loss of smell developing after upper respiratory tract infections (like the common cold or influenza) is seen in 11% to 40% of cases.³ The coronavirus causing severe acute respiratory syndrome (SARS) is known to be neurotropic.⁴ The neuroinvasive potential of SARS-CoV-2 is assumed to be partly responsible for the symptoms of respiratory failure in COVID-19 patients.⁵ Loss of smell related to neuropathy with acute onset after SARS infection and a duration of 2 years has been reported.⁶ As the target cells for the virus are located in the lower respiratory tract, COVID-19 patients show fewer upper respiratory tract symptoms.⁷

In infections with the highly contagious SARS-CoV-2, olfactory and gustatory dysfunctions emerge as the first signs of the disease, which explains their great importance from the angle of disease control. Several publications demonstrate that the SARS-CoV-2 may cause loss of smell and taste, a symptom of disease onset that develops suddenly during the course of the illness.^{5, 8–15} Rates of patients' self-reported subjective smell and taste loss range from 40% to 80%. A meta-analysis of 19 studies with a total of 10,818 patients calculated that 8823 patients had ageusia (81.6%; range 5.6%–88%) and 8088 had anosmia (74.8%; range 5.1%–85.6%).¹⁶ Both findings occurred jointly in 85% of patients.¹⁷ In addition, cases without fever and cough, with loss of smell or taste as the only complaint, have also been reported.^{18,19} These symptoms can be considered as the first signs of the infection.¹⁶ Objective smell tests found that 98% of COVID-19 inpatients participating in the study showed some olfactory dysfunction, whereas 25% of the sample suffered anosmia.¹¹ Another objective test used for chemosensory assessment showed that 73.6% of 72 patients exhibited olfactory or gustatory dysfunction; most of them were found to be hyposmic, and in one third, gustatory dysfunction was found.²⁰

However, very few data are available regarding the effect of disease severity on those findings. In a more seriously affected patient group in intensive care, loss of smell and taste amounted to 19%.²¹ A study comparing the frequency of anosmia between hospitalized patients and outpatients found a higher rate of anosmia in the outpatients (26.9% versus 66.7%, $P < 0.001$).¹⁰ However, in a study by Mao et al¹⁴ with a rate of smell or taste impairment of 5% in patients with peripheral nervous system (PNS) manifestations, no significant difference was found between mild and severe infections.

In our study, we aimed to determine the occurrence and duration of smell and taste loss among COVID-19 patients and to investigate whether a difference between outpatients and inpatients.

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MATERIALS AND METHODS

Between April and July, 2020, we evaluated consecutive adult patients examined in our COVID-19 outpatient clinic with diagnoses of mild to moderate COVID-19 who either went on to receive outpatient treatment or were hospitalized subsequently. Thus, we mainly included mild-to-moderate COVID-19 patients, defined as patients without need of intensive cares. Reported COVID-19 cases were classified as mild to moderate (ie, non-pneumonia and mild pneumonia) (Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. Vital surveillances: the epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) China Centers for Disease Control Weekly. 2020, 2(8): 113–122) The study was approved by the Ethics Committee of Istanbul Medipol University and Turkey Ministry of Health (10840098–604.01.01-E.19401; 2020–05-03T23_39_28). The patients' demographic data, clinical and radiological findings, and general and otolaryngological signs were recorded.

Enrolled in the study were patients fulfilling the following inclusion criteria:

- Being adult (≥ 18 years of age)
- Having a laboratory-confirmed COVID-19 infection (nasopharyngeal swab test – reverse transcription polymerase chain reaction, RT-PCR)
- Being clinically able to answer survey questions
- Not having suffered from olfactory or gustatory dysfunction before the pandemic
- Not suffering from chronic rhinosinusitis, nasal polyps, common cold, or influenza.

At the time of evaluation by the ENT specialist, the otolaryngological examinations of all patients included in the study were normal. Those with abnormal findings in their ENT examination were excluded from the study.

Evaluation of olfactory and gustatory function was carried out face-to-face twice at different times with self report's of patients. (in the first week of clinical disease symptoms and 21 days after the end of treatment). They answered "How would you evaluate your ability to identify odors or taste compared to nonCOVID period of your life?" (formulated comparison question). Patients not reporting any change in their sense of smell or taste in either of the interviews were grouped as normosmic-normogeusic. Those with changes in smell were classed as follows:

- Some difficulty smelling (mild hyposmia)
- Considerable difficulty smelling (moderate hyposmia)
- Cannot smell anything (anosmia)
- Perceiving smells differently (parosmia)
- Those with changes in taste were classed as follows:
- Some difficulty tasting (mild hypogeusia)
- Considerable difficulty tasting (moderate hypogeusia)
- Cannot taste anything (ageusia)
- Perceiving tastes differently (parageusia).

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, Version 24.0. (Armonk, NY: IBM Corp.). In descriptive data analysis, frequency, percentage, mean, standard deviation, and minimum/maximum values were used. Categorical variables were analyzed with chi-square and advanced chi-square tests. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Mean age of the total sample of 217 patients was 41.74 ± 12.62 years (range 18.00–76.00), 59.4% were male. Of these patients, 40.55% ($n = 88$) were hospitalized, 59.45% ($n = 129$) received outpatient treatment. Demographic and clinical characteristics of the study participants are presented in Supplementary Digital Content, Table 1, <http://links.lww.com/SCS/C282>.

The most commonly reported complaints by the patients were cough, fever, and myalgia/fatigue (in this order). The distribution of the main complaints is presented in Figure 1A.

About half the patients (53%) showed chemosensory symptoms (olfactory or gustatory dysfunction). Around one third of the patients were anosmic or ageusic (33.2%–33.1%, respectively). Rates for mild-to-moderate hyposmia and parosmia were far lower: A relatively low fraction of patients had mild-to-moderate symptoms of hypogeusia and parageusia. The detailed distribution of patients' olfactory and gustatory dysfunction is presented in Figure 1B and C.

This study found no statistically significant correlation between the presence of chemosensory symptoms and patients' complaints or severity of thorax computed tomography findings ($P > 0.05$ each). On the other hand, the presence of chemosensory symptoms in women was higher than in men ($P = 0.009$). Of all study participants, 47% had neither gustatory nor olfactory dysfunction whereas 43.32% had both.

A further analysis for olfactory dysfunction comparing outpatients and hospitalized patients determined a significantly greater frequency of anosmia in outpatients ($P = 0.038$).

Although no statistically significant correlation was observed between chemosensory impairment and other clinical characteristics, both gustatory and olfactory dysfunction in women were higher than in men ($P = 0.023$). There was no correlation between olfactory and gustatory dysfunction and age ($P = 0.178$).

Clinically, the median onset time for chemosensory symptoms was 3 (1–13) days and the median recovery time 13 (3–30) days. At 2-month follow-up, sensory impairment continues in 5 patients. Onset and recovery times for chemosensory dysfunction are presented in Figure 1D and E.

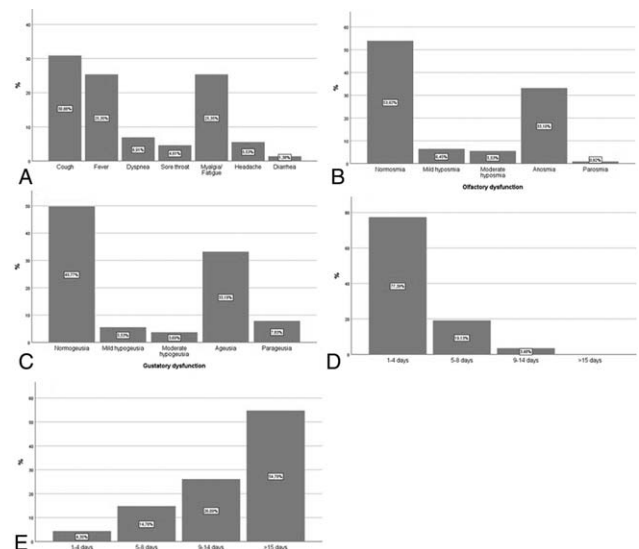


FIGURE 1. (A): Distribution of the patients' main symptoms. The ordinate axis consists of percentages of patients with these symptoms. (B): Distribution of patients' olfactory dysfunction. (C): Distribution of patients' gustatory dysfunction. (D): Symptom onset time in patients with chemosensory deficits. (E): Recovery time in patients with chemosensory deficits.

The study found no statistically significant difference between hospitalized patients and outpatients for the presence of gustatory dysfunction symptoms ($P = 0.105$ and $P = 0.513$, respectively).

DISCUSSION

Our study qualitatively evaluated olfactory and gustatory functions in patients diagnosed with SARS-CoV-2 infection, comparatively for outpatients and hospitalized patient groups, and investigated the recovery of these functions during follow-up post-treatment. The international scientific community has quickly included newly occurring anosmia or ageusia, accumulating in case reports and studies all over the world, among the main symptoms of COVID-19 infection. As contagion may occur in the early course of the infection, recognizing this kind of initial symptoms could help identifying SARS-CoV-2 in the initial stages.²² According to our study results, anosmia and ageusia were present in around half the members of the COVID-19 group. Although anosmia was a significantly more common symptom in milder cases of COVID-19 in outpatients, no difference between the 2 groups was found for gustatory dysfunction.

In many viral infections of the upper respiratory tract, smell and taste dysfunctions occur with mucosal congestion; by contrast, only very few COVID-19 patients exhibit mucosal congestion.^{8-14,23} The pathophysiological mechanisms causing impairment of smell and taste in COVID-19 are still unknown. The pathogenesis of these dysfunctions is being explained with hypotheses generated on the basis of studies with other coronaviruses.¹⁵ Although anosmia in COVID-19 may be caused directly by invasion of the olfactory pathway, it is thought that the accompanying ageusia may be related to diminished retronasal olfaction rather than direct impact on the taste receptors, as objective taste tests have confirmed.^{24,25} In cases of olfactory impairment, damage occurs at the level of chemosensory receptors.^{26,27} Cellular destruction in the olfactory neuroepithelium may lead to inflammatory changes that in turn damage neuronal function. Subsequently, olfactory receptor neurons may be damaged and neurogenesis disrupted.²⁴ The penetration of SARS-CoV-2 via the olfactory bulb is thought to be facilitated by the copious expression of the ACE-2 receptor in the epithelial cells of the oro-nasal cavity that is needed for the virus to be able to enter the cell.²⁸ Viral pathogens infecting the nasal epithelium can be transported to the central nervous system (CNS) by retrograde axonal transport along the olfactory pathway.²⁹

Giacomelli et al were able to interview 59 out of 88 hospitalized patients with COVID-19; in 20 of them (33.9%), at least one of the chemosensory modalities (smell or taste) was affected, in 11 (18.6%) both.³⁰ Females experienced these complaints more often. A case-control study employing quantitative smell testing found that almost everybody who had come in contact with COVID-19, irrespective of severe nasal congestion or inflammation, exhibited loss of smell.¹¹ Patients with olfactory or gustatory dysfunction can be asymptotically contagious. In our patient group, half of the individuals (53%) displayed chemosensory symptoms. Although 53.9% were normosmic, 33.2% were anosmic. Almost half of the 217 patients (49.8%) were evaluated as normogeusic, 33.1% as ageusic.

In the study by Mao et al¹⁴ with 214 inpatients, 36.4% showed neurologic symptoms: Symptoms of the CNS were found in 24.8%, in the PNS 8.9%, and in the skeletal muscles 10.7%. Most common complaints in patients with CNS symptoms were dizziness (16.8%) and headache (13.1%), whereas the most frequently seen complaints with PNS symptoms were hypogeusia (5.6%) and hyposmia (5.1%). In another study with 59 COVID-19 patients, the rates for olfactory and gustatory dysfunction were 68 and 71%, respectively. This rate was found to be significantly lower in 203 COVID-19-negative patients with flu-like complaints, with 16% for smell and 17% for taste. In the latter study, olfactory and gustatory

dysfunction showed a significant and strong correlation with testing positive for COVID-19, and a correlation between sore throat and COVID-negativity was also found.¹² Although the outpatients participating in our study mainly presented with complaints like fatigue/myalgia and headache, hospitalized patients mainly displayed more severe symptoms like cough, fever, and dyspnea. According to our results, there was no significant correlation between clinical complaints and chemosensory symptoms. Compared to inpatients with hospitalized patients, anosmia symptoms in outpatients were significantly more common. No difference between the groups could be seen regarding ageusia. Although the pathophysiological mechanisms causing olfactory and gustatory dysfunction in COVID-19 are not clear, severity of the disease and olfactory dysfunction appear to be inversely correlated.

In our patient group, gustatory as well as olfactory impairment was higher in women than in men. No correlation was found between smell and taste impairment and age. Although some studies reported female sex and young age as being risk factors for chemosensory loss, others did not find any difference.^{8,11,31}

The onset time for chemosensory symptoms in our patients was on average 3 days, the mean recovery time, in accordance with the literature, 2 weeks.^{8,20} Furthermore, olfactory and gustatory dysfunction could begin before the onset of general symptoms as well as simultaneously or subsequently. In 5 of the our patients, chemosensory dysfunction is still ongoing. These patients declared that only recovered up to 10% in detailed inquiries. At present, it is not possible to know if SARS-CoV-2 infections may cause permanent olfactory impairment.²² When olfactory dysfunction resolves spontaneously, specific treatment is not needed. However, if the condition continues beyond 2 weeks, therapy is to be considered.³¹ The effectivity of available treatment for loss of smell and taste in COVID-19 patients is not known. However, systemic and nasal drugs used to treat postinfectious olfactory dysfunction might potentially be beneficial for COVID-19 as well. Olfactory training should be recommended in COVID-19 patients who experience loss of smell have not yet recovered, this being strongly recommended after 1 month of the dysfunction onset.³⁵

Another aspect to be discussed is the risk, if SARS-CoV-2 becomes a latent virus in the nervous system, that patients after therapy might be affected by neurological diseases in the long term.^{32,33} A high degree of vigilance should be kept for the hypothetical role of this virus in neurodegenerative processes in recovered COVID-19 patients. Therefore, long-term follow-up of these patients is of great importance, particularly for those with persisting hyposmia.³⁴

A definitive diagnosis should not be made based on subjective assessment of chemosensory function.²⁴ Since the virus can reach surfaces in the form of an aerosol, infection via surfaces should be considered.³⁶ Due to a high risk of contagion and technical limitations, unfortunately, we were unable to perform an objective olfactory function test on patients. Vaira et al shown that on quarantined patients, the olfactory and gustatory evaluation by self-administered test can be considered a valid tool, fundamental for remotely obtaining qualitative and quantitative data on the extent of chemosensitive disorders.³⁷

This pandemic has created a need and opportunity for telemedicine. Video visits can prefer to telephone visits because they allow for better interaction and data gathering. Virtual visits have been widely accepted by patients and represent a key component of providing timely and safe health care during this pandemic.³⁸ Telemedicine not only can be valuable for patient monitoring of SARS-CoV-2 infection, but may be a helpful tool for ongoing COVID-19 olfaction research.^{39,40}

To conclude, olfactory and gustatory dysfunctions are common symptoms in COVID-19 patients not displaying signs of nasal

congestion. Newly developing anosmia or ageusia have been recognized by the international scientific community as important symptoms of COVID-19. Early isolation and testing of persons showing these symptoms can help preventing further contagion.

COVID-19-related anosmia is a new definition in medicine. Half of COVID-19 patients present with anosmia but its pathogenesis is not well understood. In many patients, anosmia is associated with dysgeusia. These symptoms may be considered as the first indication of the infection. In the absence of other respiratory disorders, such as allergic or acute rhinitis, chronic rhinosinusitis; anosmia, hyposmia, and dysgeusia will alert doctors to the possibility of COVID-19 infection and warrant serious consideration for self isolation and testing of these individuals. Recovery of olfaction and taste after the infection lasts less than 28 days.

Finally, understanding the sensorineural mechanisms of smell and taste loss in coronavirus infection might open new perspectives on viral pathogenesis.

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