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Review Article

# Olfactory Dysfunction in Patients with Coronavirus Disease 2019: A Narrative Review

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**Abstract**

**Background:** The global public health and economic systems have been severely damaged by the coronavirus disease 2019 (COVID-19) pandemic. Olfactory dysfunction (OD) is one of the most prevalent symptoms experienced by COVID-19 patients, documented in clinical practice. In some individuals, OD is the first or the sole clinical symptom. In this review, the clinical characteristics, causes, evaluation procedures, prognosis, and available treatments of COVID-19-induced OD were examined.

**Methods:** The PubMed, Scopus, Web of Sciences, and Google Scholar databases were searched for the related articles from inception until August 2022.

**Results:** OD appears to be common in COVID-19, particularly in younger individuals and women and those with milder disease. Even though the issue is still unresolved, current research suggests that COVID-19-related OD is not caused by direct injury to olfactory sensory neurons but instead is a result of indirect injury to these cells. Moreover, effective therapeutic methods are inadequate despite the high prevalence of COVID-19-related OD.

**Conclusion:** The focus of medical practice regarding COVID-19-related OD should be on identifying individuals with a poor prognosis who may benefit from early management to prevent complications, e.g., depression and anxiety, because COVID-19 OD generally has a good prognosis and quick recovery time.

**Keywords:** COVID-19, Olfactory dysfunction, Anosmia, Dysosmia, Hyposmia

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## Introduction

Coronavirus disease 2019 (COVID-19) is an infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since January 2020, COVID-19 has burdened the world's economic and public health systems (1). Fever, cough, fatigue, headache, myalgia or joint discomfort, sore throat, olfactory dysfunction (OD), gustatory dysfunction (GD), and diarrhea are among the common clinical signs and symptoms of COVID-19 (2). The focus of growing scientific interest has been on OD, which is categorized as anosmia, hyposmia, and dysosmia, and is one of the early and prevalent signs of COVID-19 (3). The idea that OD should be given significant priority as a prodromal symptom of COVID-19 stems from the fact that 40-50% of patients report OD as their first or sole symptom (4,5). OD is associated with a relatively excellent prognosis in COVID-19, in contrast to findings on infections caused by other viruses. This suggests unique pathogenic pathways that need further explanation (6). In this review, we examine the clinical characteristics, causes, evaluation procedures, prognosis, and available treatments of COVID-19-induced OD.

## Methods

The PubMed, Scopus, Web of Sciences, and Google Scholar databases were searched for the related articles published from inception until August 2022. "COVID-19", "olfactory dysfunction", "anosmia", "hyposmia", "dysosmia", and their potential derivatives were the main search terms. Of the overall 952 retrieved articles, 86 articles remained for review after the exclusion of duplicates and unrelated papers.

## Results

### *Epidemiology*

The prevalence of OD in COVID-19 patients was found to be 47.9%, based on the results of a meta-analysis of 83 studies. Additionally, 35.39%, 36.15%, and 2.53% of the cases were found to have anosmia, hyposmia, and dysosmia, respectively (7). OD diagnosis is more frequent in outpatients and females (8,9). After that Mao et al published the first report of OD in 13.8% of COVID-19 patients in China, OD was found to be a common symptom in 60-90% of patients (10-12). The reported prevalence of OD in patients dropped to 40-50% after widespread recruitment of participants (13,14).

The global scope of the pandemic has caused differences in OD prevalence among nations. According to research, the prevalence of OD was reported to range from 13.8% to 67.2% in Asia (12,15), 19.4% to 85.6% in Europe (11,16), and 19% to 68% in North America (10,17), and it was 82.4% in Brazil (9). Interestingly, OD appears to be more prevalent among people with mild-to-moderate COVID-19 than among those with severe disease (18-21). It is noteworthy that regional variations in the emphasis placed on OD, the study cohort, the evaluation methodologies, and the study design may account for the varying regional distribution of OD (22). Furthermore, self-reported tests may result in an underestimation of the prevalence of OD (23,24). In comparison to self-reported testing, it has been observed that the number of patients with OD detected using objective olfactory evaluation is 2-3 times higher (25,26).

OD can also vary in severity because of different SARS-CoV-2 strains. According to a comprehensive analysis that included research articles on the investigation of post-viral OD, viral effects on the olfactory system varied depending on the viral strain and included changes in or injury to the olfactory epithelium or the olfactory bulb (27). Compared to the D614 strain, the D614G mutation enhanced the prevalence of OD in COVID-19, according to another systematic review (28). Moreover, the timing of testing, ethnic/racial characteristics, age, gender, population density, and the severity of the disease may all have a significant role in the variation in prevalence between studies (29,30).

### *Clinical Presentation*

COVID-19 patients may suddenly acquire OD without accompanying respiratory symptoms such as sore throat, nasal blockage, or rhinorrhea (29-31). In a study conducted by Lechien et al, the prevalence of OD was found to be 81.6%, while 64.4% of the ambulatory and hospitalized patients (1363) had sore throat, nasal blockage, or rhinorrhea (18). There were no significant relationships between other nasal symptoms and OD severity (23). As a typical peripheral neuropathy of COVID-19, OD is intimately linked to GD, with multiple instances of OD and GD symptoms occurring simultaneously (32-34). According to Kaye et al, GD is a result of OD (35). However, Singer-Cornelius et al hypothesized that GD and OD are two distinct symptoms because there were no significant connections between the two conditions in objective tests (26). Numerous studies have shown a negative correlation of OD with post-admission severity and COVID-19 mortality (36,37), which is contradictory to another report on clinical outcomes (38). In order to detect asymptomatic COVID-19 carriers, a rising number of studies have concentrated on the quantitative assessment of olfactory function (39,40). A high-impact and low-cost technique for universal screening and monitoring of COVID-19 could be a standardized quantitative test for olfactory function (41).

### *Risk Factors*

Female patients appear to be more susceptible to COVID-19-induced OD (6,8,11,42); however, according to Meini et al, OD lasts longer but occurs less frequently in female patients. This gender-based disparity may be explained by the fact that men and women experience inflammation in their bodies in different ways (43).

As for age, OD appears to occur more frequently in the younger population. In other words, the prevalence of OD has been reported to reduce with increasing age (16,19). Nevertheless, individuals over 65 years of age were found to have a two-fold increased risk of OD and people over 75 years of age had a three-fold increased risk of OD (44).

On the other hand, based on statistics, Caucasians have a 3- to 6-fold higher prevalence of OD compared with Asians and African-Americans (45,46). The identification of putative risk factors of OD requires the use of large-scale clinical samples. Obesity, hypertension, diabetes mellitus, and cardiovascular disease are the most frequently reported comorbidities in OD patients (47,48).

### *The Underlying Mechanisms of OD in COVID-19 Patients*

OD can be caused by a variety of viral infections, but the high prevalence and speedy recovery of OD induced by SARS-CoV-2 infection point to a unique mechanism (49). SARS-CoV-2 can be transmitted by the angiotensin-converting enzyme 2 (ACE2). The serine protease TMPRSS2 is used to prime the spike protein, which aids in the entrance of SARS-CoV-2 into the host cells (50-52). ACE2 is significantly linked to OD in SARS-CoV-2 infection (52,53). Data from several investigations have offered fresh insights, despite the fact that the underlying mechanisms of OD in COVID-19 are not fully understood. The present theory holds that various pathways contribute to OD caused by SARS-CoV-2 (54).

Olfactory development in the central nervous system (CNS) primarily involves the olfactory bulb, olfactory field, and limbic areas. Patients with COVID-19 have been reported to have significantly greater bilateral gray-matter volumes in their olfactory cortices, hippocampi, insulas, and left Rolandic operculum, as well as an overall drop in the diffusivity of their white matter (55). Coronaviruses can enter the CNS hematogenously or transneuronally. In a post-mortem investigation, the cerebrum of the infected patients contained SARS-CoV-2 antigens and RNA (56). SARS-CoV-2 RNA and protein have been found in anatomically separate areas of the nasopharynx and brain, according to research by Meinhardt et al. They suggested that SARS-CoV-2 might enter the CNS by crossing the neural-mucosal interface in olfactory mucosa (57). These fresh discoveries advance our knowledge of how

SARS-CoV-2 and the brain interact. It is unclear, though, whether COVID-19-induced OD is caused by the viral infection of the CNS through the olfactory system (58). At first, it was thought that SARS-CoV-2 might directly infect olfactory neurons in the CNS, resulting in OD. However, later research revealed that the olfactory neurons of the olfactory bulb did not express ACE2 (56,59).

SARS-CoV-2 RNA can be detected in the upper respiratory tract in the early stages of SARS-CoV-2 infection, suggesting active infection and replication in this area (60). Single-cell RNA sequencing datasets from healthy individuals generated by the Human Cell Atlas Consortium showed that respiratory and intestinal epithelial cells have varied amounts of ACE2 and TMPRSS2 protease expression, with the nasal epithelium exhibiting the greatest levels (61). Immunostaining of human nasal epithelial tissues revealed considerably more ACE2 expression in the olfactory epithelium compared to the respiratory epithelium. The absence of ACE2 in olfactory neurons, however, was discovered in a mouse model (62,63). Nonetheless, a sharp dot-like ACE-2 expression was detected in olfactory neurons in addition to an evident high expression of ACE2 in the sustentacular cells of human olfactory mucosa samples, suggesting potential direct neuronal injury (64).

### *Diagnosis*

COVID-19-induced OD can either be evaluated by subjective methods through questionnaire surveys or by objective methods using olfactory sensitivity test (64). Visual analogue scales and questionnaires are the methods used for subjective evaluation. Visual analogue scales are easy-to-use and reliable methods for determining whether or not olfactory function is present (5). A pen-like odor-dispensing device is used for testing the nasal chemosensory performance. The likelihood of OD in COVID-19 has doubled as a result of this test (65,66). This test can provide an accurate reflection of a person's level of olfactory function. However, it lacks specificity, making it challenging to do specific analyses related to the disease stage and treatment strategy (66).

### *Prognosis*

COVID-19-induced OD has a good prognosis and high likelihood of recovery. After four weeks of follow-up, 89% of COVID-19 patients with OD experience total remission or improvement (67,68). The mean recovery time of OD caused by COVID-19 was 7.21 ± 12.93 days according to a recent meta-analysis (13). There were no significant gender differences in the recovery of OD; nonetheless, older and female patients required more time to recover from OD (69). A number of individuals had sluggish healing or prolonged OD, which had serious detrimental impacts on their quality of life and morbidity in the form of disturbed eating patterns, social anxiety, or depression (70-72). The region, ethnicity, gender, age, and length of therapy all have an impact on OD rehabilitation (54).

### *Treatment*

Olfactory training is an effective strategy to control OD caused by a variety of reasons. Olfactory training can dramatically lessen OD caused by viral infections (73-75). It is also advised for treating COVID-19-related OD (73). Patents' olfactory function has been demonstrated to be improved using oral or topical corticosteroids. Early research, however, included people who had rhinitis and sinusitis, which are localized nasal inflammations (76-78). Furthermore, additional investigations indicated that oral or topical corticosteroids had no discernible effects on OD (79,80). Additionally, there are not enough high-quality trials showing that oral or topical corticosteroids are effective in treating OD unrelated to sinonasal disease (81). In contrast to other viral infections, OD due to COVID-19 is not substantially associated with nasal symptoms. Therefore, it is not advised to regularly use oral or topical corticosteroids for OD in COVID-19 (82,83).

Multiple medications, including theophylline, vitamin A, caroverine, intranasal sodium citrate, minocycline, alpha-lipoic acid, zinc sulfate, and Ginkgo biloba have the ability to treat OD (82-85). Most of these medications are not advised for normal use because of the paucity of clinical data on their effectiveness in COVID-19-related OD, with the exception of one case report on vitamin A (86).

## Conclusion

OD appears to be common in COVID-19 cases, particularly in younger individuals and women and those with milder disease. Even though the issue is still unresolved, current research suggests that COVID-19-related OD is not caused by direct injury to olfactory sensory neurons but instead is a result of indirect injury to these cells. Moreover, effective therapeutic methods are inadequate despite the high prevalence of COVID-19-related OD. The focus should be on identifying individuals with a poor prognosis who may benefit from early management to prevent complications, e.g., depression and anxiety, because COVID-19-related OD generally has a good prognosis and quick recovery time.

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**Competing Interests**

The author declares that he has no competing interests.

**Ethical Approval**

Not applicable.

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**Informed Consent**
Due to the nature of this study, a narrative review, informed consent was not required.

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