



Review Article

## Effect of COVID-19 on oral mucosa: Literature review

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### ABSTRACT

Severe acute respiratory syndrome coronavirus (SARS-CoV-2) is the virus that causes coronavirus disease 2019, known as Corona virus disease (COVID-19). It is a virus that affects several human organs, including the oral cavity. Human cells are more prone to the entry of SARS-CoV-2 virus due to the extensive expression of Transmembrane Proteases Serine (TMPRSS2 and TMPRSS4) and angiotensin-converting enzyme II (ACE2) receptors in various bodily tissues and organs. Due to the high expression of ACE2 receptors, it is thought that the oral cavity is particularly vulnerable to SARS-CoV-2 infection. As a result, a large number of clinical characteristics of oral manifestations have been reported in COVID-19 cases. The several oral symptoms of COVID-19, their prevalence, and a succinct explanation of their etiology are all reviewed in this article.

**Keywords:** COVID-19, Oral manifestations, Dysgeusia, Vesiculobullous, Melkersson-Rosenthal syndrome

### INTRODUCTION

Coronaviruses (COVs) are a subfamily of Coronavirinae in the family of Coronaviridae that further falls under the series of *Nidovirales*<sup>[1,2]</sup> and are mainly responsible for respiratory diseases like causing pneumonia in humans.<sup>[3,4]</sup> So far, seven COV species are known to infect human beings to name are Middle-East Respiratory Syndrome COV (MERS-CoV), HCoV NL63, HCoV 229E, HCoV OC43 and HCoV Hku1, and Severe Acute Respiratory Syndrome COV (SARS-CoV).<sup>[5,6]</sup> In immunocompetent individuals, species such as HCoV 229E, HCoV NL63, HCoV-HKU1, and HCoV-OC43 cause cold symptoms. Severe respiratory infections and mortalities are caused by MERS-COV and SARS-CoV, respectively.<sup>[5]</sup> SARS-CoV-2 is the main causative virus for COVID-19.

Airborne droplets, direct touch with an infected individual, or contact with a contaminated surface were the three ways that this virus was spread.<sup>[2]</sup> The disease spread throughout the country and became a pandemic at the end of 2019.<sup>[4]</sup> The World Health Organization (WHO) declared a major public health concern after the outbreak of MERS-COV and SARS-CoV in the year 2002 and 2012, respectively. There were over 772,052,752 COVID-19 instances globally as of the end of November 2023, and 6,985,278 million deaths had been confirmed.<sup>[7]</sup> Human beings of different races and geographical conditions infected with the COVID-19 virus manifest varying clinical signs and symptoms in various body parts, including the oral cavity. These symptoms can vary from asymptomatic to acute respiratory distress syndrome, multiorgan failure, and in extreme cases, death.<sup>[8]</sup> Fever, dry cough, fatigue, headache, diarrhea, and conjunctivitis of varying severity are the systemic manifestations of COVID-19-positive individuals.<sup>[8-10]</sup> However, due to the high level of angiotensin-converting enzyme II (ACE2) expression identified in the

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saliva of COVID-19-positive individuals, the oral cavity is more vulnerable to SARS-CoV-2 infection.<sup>[10]</sup> These individuals have dry mouth, aphthous ulcer, depapillated tongue, necrotized gingiva, taste-sensation problems, and salivary gland infections.<sup>[11,12]</sup> In the elderly, poor oral hygiene, immunosuppression, opportunistic infections, vasculitis, stress, and an increased inflammatory response can be considered as the foremost reasons for the development of oral lesions in COVID-19 infected patients.<sup>[13]</sup>

Since the plethora of oral lesion presentations such as ulcers, dry mouth, loss of taste sensation, and many more in the initial days of the disease support in diagnosis, dentists are extremely important in the diagnosis of COVID-19 infection.<sup>[14]</sup>

To the best of our knowledge, few systematic reviews specifically address the prevalence or pathogenesis and oral manifestation of COVID-19 along with its prevalence in every lesion. Hence, we aim to review and evaluate the prevalence along with oral manifestations of SARS-CoV-2 and summarize all how COVID-19 may influence the oral health of individuals. This will also lead to an immense improvement in the oral health of vulnerable hospitalized patients.<sup>[15]</sup>

## MATERIALS AND METHODS

Related full text research papers published in Medline/ PubMed, SCOPUS, Web science, and Google Scholar indexed Database from 2019 onwards were searched for inclusion in the present literature review.

The Medical Subject Heading (MeSH) terms used for literature search in search engine work COVID-19 AND/OR Oral Manifestations, COVID-19 Hospitalization, SARSCOV-2 AND/OR Oral Manifestations.

Relevant paper in English language on the topic and abstract on particular literature after excluding duplication, animal studies were thoroughly scrutinized and finally included in this narrative review. Manual search from print journal and latest edition of textbook were also searched for additional information.

## RESULTS AND DISCUSSIONS

### Oral manifestations of COVID-19

COVID-19 has impacted every aspect of society and is currently the focus of attention in both developed and developing countries.<sup>[16,17]</sup> When WHO declared COVID-19 as a pandemic disease in March 2020, the research related to it surged, and so did the publications. A variety of symptoms related to SARS-CoV-2 infection have been identified in the oral cavity. These symptoms include taste loss, dry mouth,<sup>[15]</sup> and oral cavity lesions such as ulcers

resembling aphthous, Koplik's and Nagayama's spot, papulovesicular or maculopapular lesions, red/white patches, edematous gingiva, lip swelling, and petechiae. There may be involvement of both non-keratinized (labial and buccal mucosa) and keratinized (Hard palate, Gingiva, and Dorsum of tongue) mucosa.<sup>[13]</sup>

Various publications have mentioned that the SARS-CoV-2 receptor-binding domain has a strong affinity for ACE2-functional receptors. The lining mucosa of the nose, lung pharynx, oral mucosa, salivary glands, and several human organ systems are all ACE2-rich, which makes them both susceptible to viral damage and a portal for viral entry into the body. As a result, three categories could be used to discuss the various oral manifestations of COVID-19 that have been documented in the literature and reviewed here.<sup>[10]</sup>

- Category 1 – Due to direct link to SARS-CoV2 infection [Table 1]
- Category 2 – Due to coinfection secondary to SARS-COV-2 therapy [Table 2]
- Category 3 – Due to immunologic abnormalities in hospitalized patients [Table 3].

### Oral manifestation due to direct link to SARS-COV-2 infection

**Table 1:** Oral manifestations due to direct link to SARS-CoV-2.

S. No.	Oral lesion	Prevalence (%)	References/ study
1	Xerostomia	69.8, 53	2020, 2023 <sup>[10,19]</sup>
2	Taste impairment	87, 60	2020, 2022 <sup>[20,21]</sup>
3	Burning mouth syndromes	22.4, 28.5	2022, 2023 <sup>[24,27]</sup>
4	Ulcerative lesion (herpetiform, aphthous like ulcer, vesiculobullous, and maculopapular)	20.4, 54	2021, 2023 <sup>[19,21]</sup>
5	Mucositis	3.9	2021 <sup>[23]</sup>
6	Erosion	50	2022 <sup>[10]</sup>
7	Petechiae	11, 7.4	2022, 2023 <sup>[34, 18]</sup>
8	Blisters	12.6	2022 <sup>[37]</sup>
9	Macules	50	2022 <sup>[10]</sup>

SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2

**Xerostomia:** The most prevalent cause of decreased saliva output was infection with SARS-CoV-2. In addition to their main complaint of dry mouth, patients with xerostomia often reported experiencing other symptoms such as dysgeusia, angular stomatitis, and a burning sensation in the oral cavity.<sup>[16]</sup> In the ductal epithelial cells and acinar of the salivary glands, Fakhruddin *et al.* demonstrated the abundant expression of ACE2 and transmembrane protease serine receptors for SARS-COV-2, which results in a reduction in salivary production and oral cavity infections.<sup>[10]</sup> In the studies conducted by Tuter

*et al.* (2022),<sup>[8]</sup> Fakhruddin *et al.* (2022),<sup>[10]</sup> Fantoozi *et al.*<sup>[18]</sup> Fernandes *et al.*<sup>[19]</sup> the frequency of dry mouth was found to be 47.6%, 69.85, 45.6%, and 53%. Throughout all these studies, xerostomia was the most common oral symptom among COVID-19 patients, and it did not statistically differ between patients in different age groups.

**Taste buds/tongue impairment:** Studies conducted on the prevalence of tongue impairment by different authors; Sinjari *et al.*,<sup>[20]</sup> Fantoozi *et al.*,<sup>[18]</sup> Vallarrol Doreggo *et al.*,<sup>[21]</sup> found 25%, 87%, 60% of prevalence, respectively. According to almost all published studies, research indicates that the different types of taste disorders, which includes ageusia, hypogeusia, and dysgeusia, is most often caused by increased proliferation and hypertrophy of the tongue's filiform papillae, which results in a metallic taste, in addition to a lack of desquamation.<sup>[22]</sup>

**Burning mouth syndrome:** According to Fakhruddin *et al.* (2022), the majority of individuals with altered taste disorder and dry mouth report a burning mouth sensation.<sup>[10]</sup> However, the burning mouth feeling is a fairly general disease that can be linked to a wide range of other conditions, such as mental health issues, mineral or vitamin deficiencies, diabetes, candidal infections, and various medications. Few more studies conducted by authors Nuno-Gonzalez *et al.*,<sup>[23]</sup> El-Kady *et al.*,<sup>[24]</sup> El Tantawi *et al.*,<sup>[25]</sup> Mohammad *et al.*,<sup>[26]</sup> and Al- Magsoosi *et al.*<sup>[27]</sup> show the prevalence of burning mouth syndrome in 5.3%, 22.4%, 13.1%, 22.5%, and 28.5% of cases, respectively.

**Ulcerative lesion:** Among all patients examined for COVID-19, oral ulcers were the most prevalent lesion.<sup>[10]</sup> The common source of all the diseases is thought to be host's defense system response to viral antigenic components of the mucosal epithelium, or abnormalities in the oral mucosa's superficial epithelial barrier caused by viral invasion.<sup>[10]</sup> Gheolone *et al.*,<sup>[28]</sup> Abubakr *et al.*,<sup>[29]</sup> Tuter *et al.*,<sup>[8]</sup> Fernandes *et al.*,<sup>[19]</sup> and observed ulcers in 12%, 20.4%, 14.5%, 54%, of cases, respectively.<sup>[8,21]</sup>

Brandao *et al.*<sup>[30]</sup> Chaux-Bodard *et al.*,<sup>[31]</sup> and Ciccarese and Demirbas *et al.*<sup>[32]</sup> have described different types of an ulcer like herpetiform, aphthous-like ulcers, vesiculobullous, and maculopapular in COVID-19 patients.

**Angina bullosa:** According to Fakhruddin *et al.* (2022), angina bullosa is an inflammatory response caused by SARS-CoV-2 and is considered to be a symptom of thrombus formation and subsequent vascular endothelial failure.<sup>[10]</sup> According to Favia *et al.*<sup>[33]</sup> and AL- Mastroogi *et al.*,<sup>[27]</sup> the prevalence of angina bullosa was 8.42% and 14.5 % respectively reported in COVID-19 investigations.

**Petechiae:** Iranmanesh *et al.* (2021)<sup>[13]</sup> stated that the palate, oropharynx mucosa, and lower lip all had petechiae. One possible cause of this could be COVID-19-related

**Table 2:** Oral manifestation of COVID-19 secondary to SARS-CoV-2.

S. No.	Oral lesion	Prevalence (%)	References/study
1	Angina bullosa	8.42, 14.5	2020, 2023 <sup>[27,33]</sup>
2	Petechiae	11, 7.4	2022, 2023 <sup>[19,34]</sup>
3	Candidiasis	70.7	2022 <sup>[35]</sup>

SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2,  
COVID-19: Coronavirus disease 2019

thrombocytopenia.<sup>[10]</sup> Patients with petechiae had a shorter latency period.<sup>[13]</sup> Some authors as Binmadi *et al.*,<sup>[34]</sup> and Fernandes *et al.*<sup>[19]</sup> observed 11%, and 7.4% of prevalence, respectively.

### Oral manifestation of COVID-19 due to co-infection secondary to SARS-COV-2

**Fungal infections:** Even after the COVID-19 signs and symptoms have subsided, opportunistic fungal infections may result from generalized immunosuppression.<sup>[10]</sup> Among COVID-19 patients, the most prevalent fungal infections found are candidiasis, mucormycosis, and aspergillosis.

**Candidiasis:** Fakhruddin *et al.* have stated that *Candida albicans* is the most prevalent causative yeast for mucosal candidiasis, which is very likely to occur in COVID-19 patients.<sup>[10]</sup>

In diabetic patients receiving SARS-CoV-2 treatment, there has been a notable increase in the incidence of angioinvasive maxillofacial fungal infections, which has been linked to corticosteroid medication.<sup>[14]</sup> Sharma *et al.* (2022) conducted a study on 18 cases of COVID-19 patients and observed 16 patients with mucormycosis, followed by one patient with aspergillosis and one patient with mixed fungal infection.<sup>[14]</sup> Other studies by Selehi *et al.*<sup>[35]</sup> observed a 70.7% high risk of *C. albicans*. Oral pseudomembranous candidiasis was another common fungal lesion observed in studies conducted by Bardellini *et al.*<sup>[36]</sup> and Binamdi *et al.*,<sup>[34]</sup> they found prevalence in 7.4%, and 27% of cases, respectively.

**Mucormycosis:** Mucormycosis, often referred to as "black fungus disease," is a somewhat frequent presentation that has mostly been recorded from the Indian subcontinent. Following recovery from COVID-19, it may manifest as mouth ulcerations.<sup>[10]</sup>

**Aspergillosis:** Pulmonary aspergillosis is the third most prevalent fungal illness found in COVID-19 patients.<sup>[10]</sup>

**Mucositis:** Mucositis due to thrombotic vasculopathy, vasculitis, or virus-related hypersensitivity is observed as secondary lesions after COVID-19 infection.<sup>[13]</sup> Almost 3.9% of similar cases were observed in the study carried by Nuno-Gonzalez *et al.* (2021).<sup>[23]</sup>

**Table 3:** Oral manifestations due to immunologic abnormalities (hospitalized bound patients).<sup>[10]</sup>

S. No.	Oral lesion	Prevalence (%)	References/ study
1	Ulceronecrotic gingivitis	6	2022 <sup>[37]</sup>
2	Fungal infection (mucormycosis)	70.7	2022 <sup>[35]</sup>
3	Gingivitis	93.7, 22.7	2021, 2023 <sup>[19,38]</sup>
4	Periodontitis	49.4, 4	2021, 2022 <sup>[34,38]</sup>
5	Desquamative gingivitis	7.3	2022 <sup>[39]</sup>
6	Halitosis	10.5	2021 <sup>[29]</sup>
7	Glossitis	9.3	2022 <sup>[19,37]</sup>
8	Mucormycosis	4.5	2023 <sup>[22]</sup>
9	Depapillation	9.5	2022 <sup>[15]</sup>
10	Angular cheilitis	9.5	2022, 2023 <sup>[22,48]</sup>
11	Mickelson-Rosenthal syndrome	1	2022 <sup>[14]</sup>

**Oral manifestation due to immunologic abnormalities in hospitalized patients**

**Necrotizing-ulcerative gingivitis (NUG):** In study conducted by Iranmanesh *et al.* and Erbas *et al.* in the year 2021 and 2022, the patients examined for COVID-19 presented with NUG in the oral cavity, the lesions were edematous, unpleasant, and diffusely erythematous in necrotized interpapillary areas.<sup>[13,37]</sup>

**Gingivitis:** According to Fernandes *et al.* 2023, the serious consequences of COVID-19 cause a lack of proper oral hygiene measures, which contribute to the development of gingivitis. Gingivitis emphasizes the necessity of improving oral health awareness and maintaining appropriate oral hygiene practices.<sup>[19]</sup> The authors Anand *et al.* in<sup>[38]</sup> and Fernandes *et al.*<sup>[19]</sup> show a prevalence of cases of gingivitis in 93.7% and 22.7% of cases, respectively.

**Periodontal health/periodontitis:** Literature of Frenandes *et al.*<sup>[19]</sup> has described a severe and rapidly progressing disease that affects free, attached gingivae or the alveolar mucosa, causing ulceration, discomfort, necrosis, and bleeding.<sup>[19]</sup> The illness can develop as a consequence of chronic gingivitis in debilitated individuals or immunocompromised patients. In general, the condition was observed in several critically ill COVID-19 patients who have poor oral hygiene.<sup>[10]</sup> Marouf *et al.*,<sup>[40]</sup> Binmadi *et al.*,<sup>[34]</sup> and Anand *et al.*<sup>[38]</sup> observed prevalence of cases of periodontitis in 44%, 4%, and 49.4% of case, respectively.

**Halitosis:** Halitosis is an expressing state for a range of systemic illnesses, including respiratory, otolaryngologic, and gastrointestinal pathologies, that may affect salivary features and tongue dorsum susceptibility to host anaerobic microbes. According to the study of Riad *et al.*,<sup>[41]</sup> the COVID-19 has posed a significant threat to halitosis, with a small number of confirmed individuals presenting with halitosis.<sup>[41]</sup> Abukhar

*et al.*,<sup>[29]</sup> Bullet *et al.*,<sup>[42]</sup> Muthyan<sup>[43]</sup> observed 10.5 %, 21%, 2% cases of halitosis respectively.

**Melkersson-Rosenthal syndrome:** Melkersson-Rosenthal syndrome is characterized by hyperemic lower lip with firm edema spreading to the jaw, right facial paralysis, and fissured tongue. It was determined that activated mast cells, which produce cytokines in the lungs, may play a substantial role in the pathogenesis of COVID-19 infection and may be a potential etiological cause for this presentation.<sup>[14]</sup>

**Tongue coating:** Literature suggested that abnormal tongue-coating patterns were seen in COVID-19 patients.<sup>[44]</sup> These coating patterns are linked to inflammatory responses and can provide insight into the course of the illness. The most often reported subjective signs of lingual involvement were red tongue, yellow, greasy, white coating, greyish-black coating, spots, spikes, and tooth-marked tongue. It is interesting to note that individuals with fewer cases of COVID-19 had tongues that were thinner and lighter in color. On the other hand, thicker coatings, more painful tongues, and purple tongues were seen in patients with more severe instances.<sup>[22]</sup>

During the COVID-19 pandemic, tongue villosa nigra, or BHT, is commonly observed in individuals with extrapulmonary function.<sup>[22]</sup> The prevalence of tongue coating observed in the study conducted by Naser *et al.*,<sup>[45]</sup> Eduardo *et al.*,<sup>[46]</sup> Fernandes *et al.*,<sup>[19]</sup> and Natto *et al.*<sup>[47]</sup> showed tongue coating in 4.7%, 3%, 7.4%, and 7.3%, respectively.

**Angular cheilitis:** Angular cheilitis is an inflammatory condition that appears as approximately triangular lesions at the labial commissures. Its typical symptoms are red, edematous, and frequently painful patches of skin; mild instances may just exhibit some reddish erythema with neighboring lips that are either normal or chapped.<sup>[48]</sup>

**SUMMARY AND CONCLUSION**

In March 2020, the World Health Organization announced COVID-19 as the fifth pandemic illness. Since then, several oral symptoms caused by COVID-19 exposure have been observed. The appearance of lesions and symptoms in the oral cavity vary depending on the type of SARS CoV- 2 exposure. In the present review, we can conclude that the high prevalence of oral symptoms and manifestations directly linked to SARS CoV-2, as taste alteration, dry mouth, oral ulceration, and burning mouth sensation could be appreciated in COVID-19 patients. Oral manifestations due to COVID-19 secondary to SARS CoV-2 were candidiasis, followed by angina bullosa and petechiae, and other manifestations like gingivitis and periodontitis were also appreciated in a hospitalized bound patient. Recognizing COVID-19 signs and symptoms is critical for early diagnosis and a better prognosis. As a result, dental practitioners should be aware of the signs and symptoms and can play an important role in routine oral examinations,

not only in preventing COVID-19 transmission but also in stopping the disease progression.

### Ethical approval

The Institutional Review Board approval is not required.

### Declaration of patient consent

Patient's consent is not required as there are no patients in this study.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

### Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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