

# Oral lesions associated with COVID-19: A systematic review

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## SUMMARY

**Background.** Oral lesions has been reported in coronavirus disease 2019 (COVID-19). However, there are gaps about the occurrence. The aim of this study was to describe the clinical characteristics of oral lesions in patients with COVID-19.

**Methods.** A systematic review was conducted in four electronic databases (PubMed, Lilacs, Cochrane and Google Scholar) with the search terms: “coronavírus”, “COVID-19”, “SARS-CoV-2”, “novel coronavírus”, “2019nCoV”, “oral manifestation”, “mucosal lesions”, “oral lesions”, “mucosa viral lesions” and “oral conditions”. Articles were limited to those published between january and july 2020, and in English.

**Results.** Initially, 182 articles were found, after reading the titles and abstracts a total of 24 records were included for full-text reading. Finally, 22 articles were included for data extraction and assesment. We identified and subsequently discussed clinical characteristics and differential diagnosis.

**Conclusions.** The etiology of many oral mucosal lesions is intimately related to infectious, immunological, and psychosocial factors. Therefore, amid the SARS-CoV-2 pandemic in which many doubts about the disease still remain, caution is needed when evaluating patients and establishing correlations with other diseases that could be associated.

**Keywords:** COVID-19, oral manifestations, oral lesions.

## INTRODUCTION

In December 2019, the first cases of pneumonia were reported in the city of Wuhan, China. Wuhan has a large local fish and wildlife market and almost all reported cases had a history of contact with the city, a fact that led researchers believe that the infection may have been transmitted by bats sold on this market (1). The disease was called coronavirus disease 2019 (COVID-19). Shortly thereafter, by February 15, COVID-19 started to spread rapidly across China. Thailand and Japan were the countries outside China to confirm the first cases of the disease on February 12 and 16, respectively. Since then, the virus has spread to other regions of Europe, Asia, South America, North America, Oceania and Africa. On March 11, the World Health Organization declared COVID-19 a pandemic (2).

The early symptoms of COVID-19 resemble those of other infectious diseases and include the presence of fever, fatigue, dry cough and shortness of breath, which are considered common/mild symptoms (3). Other symptoms found in patients with the disease include pneumonia, acute respiratory distress syndrome, difficulty breathing, persistent chest pain or pressure, confusion, difficulty waking up, bluish face or lips, muscle pain, sputum production, diarrhea, loss of smell and taste, abdominal pain, nausea, vomiting, chest tightness and palpitations, upper airway symptoms such as sneezing, a runny nose or sore throat, hemoptysis, headache, septic shock, metabolic acidosis and coagulation dysfunction, which are regarded more severe clinical manifestations (1, 2, 4).

In addition to these symptoms, some signs can be found in patients who manifest the disease. The first study on the presence of skin and mucosal lesions in patients with COVID-19 was published by Galvan Casas *et al.* (5) in April 2020, which included 375 patients treated for COVID-19 in Spain who exhibited five different patterns of skin lesions. These authors

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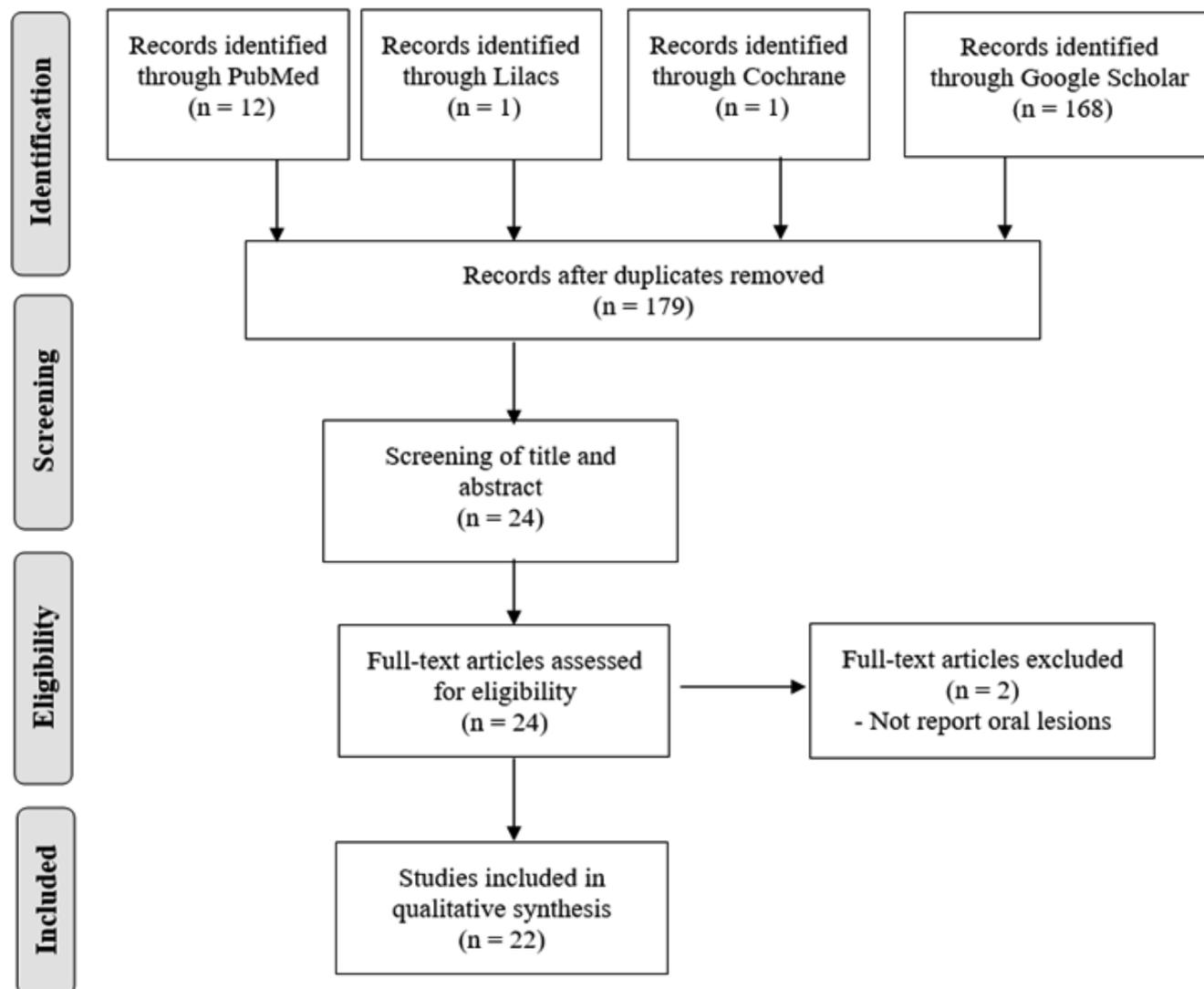


Fig. PRISMA flow diagram of literature search

also published an atlas containing the images of these different patterns. Some lesions were identified in the oral mucosa of two patients who had enantheis involving the palate and gingival margins.

In May 2020, Chaux-Bodard *et al.* (6) reported the first case of an oral lesion in a patient diagnosed with COVID-19. This case raised several questions regarding the origin of the lesion and the possibility that these lesions are caused by infection with SARS-CoV-19. Therefore, amid the growing number of cases of the disease in the world, the aim of this study was to conduct a literature review on the presence of oral lesions in patients with COVID-19, emphasizing the importance of assessing the oral cavity of patients diagnosed with the disease.

## METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic

Reviews and Meta-Analyses (PRISMA) Statement (7). The following research question was defined using the PICO strategy: “Which are the most common oral lesions in patients with COVID-19?”.

A full search strategy was adopted, including the following MeSH terms and no-MeSH terms: “coronavirus”, “COVID-19”, “SARS-CoV”, “novel coronavirus”, “2019nCoV”, “oral manifestation”, “mucosal lesions”, “oral lesions”, “mucosa viral lesions”, and “oral conditions”. The search was performed in four databases: PubMed, Google Scholar, Lilacs and the Cochrane Library. A search strategy using the Boolean operators AND and OR was developed to identify relevant articles in each database.

The search was performed between July 7 and 21, 2020. Articles published in English were analyzed and only those published as of January 2020 were considered. After the search, the references found in the databases were exported to the

Mendeley® program to identify duplicate articles.

Duplicates were removed and the studies were selected based on the title and abstract. The articles were screened by two authors and the eligibility of the studies was evaluated independently. Disagreements were resolved by a third author.

In view of the scarce evidence, original articles, editorials, letters and reviews providing data on oral lesions in patients infected with SARS-CoV-2 were included in the study.

## RESULTS

The final electronic search provided 12 from PubMed, 168 from Google Scholar, 1 from Lilacs, and 1 from the Cochrane Library. PRISMA flow diagram of literature search (Figure) summarizes the study selection process. Of the 22 articles retrieved by the search strategy, three were case reports, 15 were letters to the editor (7 reporting a case), two were reviews, and two were comments. These studies referred to 16 patients, most of them males, whose age ranged from 6 to 75 years.

The first case of an oral lesion in a patient diagnosed with COVID-19 was reported by Chaux-Bodarb *et al.* (6), who described an ulceration on the dorsal side of the tongue that developed after a macular erythematous lesion, which might be attributed to vasculitis. Subsequently, Martin Carreras-Presas *et al.* (8) reported three cases; two patients had ulcerated lesions in the oral mucosa but they were not tested for the confirmation of COVID-19. In the third case, the patient was admitted for the treatment of pneumonia due to SARS-CoV-2 and received antibiotic, antiviral agents and corticosteroid. The patient developed macular lesions on the skin 4 days after discharge. These lesions were followed by the development of lower lip mucosal blisters and desquamative gingivitis.

Sinadinos and Shelswell (9) reported the cases of two patients with a suspicion of COVID-19 who had ulcerated lesions in the oral mucosa that resembled recurrent herpes. In the third case, the patient developed desquamative gingivitis and blisters in the lip mucosa while hospitalized for the treatment of pneumonia caused by infection with SARS-CoV-2.

Ansari *et al.* (10) also found ulceration as oral lesion in their patients with COVID-19. In the two cases reported, the authors found several painful ulcers with irregular margins and varying sizes on a red and non-hemorrhagic background involving the palate and tongue. In the study of Soares *et al.* (11) in addition to a painful ulcerated lesion, oral

examination of the patient showed multiple red macules of different sizes spread across the hard palate, tongue and lips.

Demirbas *et al.* (12) described the case of a patient treated for COVID-19 who had erythema multiforme characterized by painful ulcerations on the lip, tongue and palate, as well as skin lesions. The authors suggested that the drugs used for the treatment of COVID-19 might have potentiated the cutaneous reaction induced by SARS-CoV-2. Labe *et al.* (13) reported the case of a 6-year-old child who tested positive for COVID-19 and whose clinical symptoms suggested the diagnosis of erythema multiforme. However, the child did not use any medication and serology was negative for *Mycoplasma pneumoniae* and herpes simplex virus, which are some of the infections that can trigger erythema multiforme in children. The authors suggested that erythema multiforme was associated with SARS-CoV-2 infection.

Kahraman and Çaşkurlu (14) reported as clinical manifestations petechiae in the midline and numerous pustular enanths near the soft palate border in a patient with a diagnosis of COVID-19, while Amorim dos Santos *et al.* (15) described persistent white plaque and multiple yellow ulcers on the back of the tongue. Ulcerations, erosions and petechiae in the oral mucosa were described by Ciccamese *et al.* (16) in a 19-year-old patient with thrombocytopenia associated with COVID-19. The patient had similar lesions on the lower limbs.

Patel and Woolley (17) described the development of necrotizing periodontal disease in a patient with a suspicion of COVID-19 who presented with erythematous and edematous gingivae and necrotic interdental papillae, suggesting that the severity of the disease may be associated with bacterial coinfections in COVID-19 patients. According to Riad *et al.* (18), reports on the onset of oral lesions in patients with COVID-19 vary widely and standardized diagnostic and assessment methods are lacking. Dziedzic and Wojtyczka (19) suggested that the onset of these lesions is associated with the complex effects of the virus and with the intensified therapies and multidrug treatments that trigger oral pathological conditions mainly related to immune mechanisms.

Pedrosa *et al.* (20) alerts that oral ulcers or blisters can be early signs of COVID-19 but how they emerge is not fully understood, a fact that may lead to erroneous conclusions. Since oral findings are still recent in the literature and their occurrence varies significantly among patients with COVID-19, associated systemic diseases and/or oral health problems can be a contributing factor to oral manifestations.

Abu-Ammad *et al.* (21), Ponce and Tijoe (22) and Rocha *et al.* (23) highlights that the association between COVID-19 and oral lesions should be interpreted and described with caution, as many viruses exists that can cause lesions in the oral cavity. In addition, COVID-19 shares many nonspecific characteristics with other respiratory diseases (18). According to Rocha *et al.* (24) and De Carvalho *et al.* (25), within the context of the COVID-19 pandemic, it is important that health professionals, especially dentists, faced with oral mucosal lesions establish the differential diagnosis with the main viral diseases that have similar characteristics. For example, oral manifestations can be caused by reactivation of the herpes simplex or herpes zoster virus, with many of the lesions observed in COVID-19 patients being similar to the herpes lesions found in daily dental routine, as suggested in the published reports.

Many drugs are also associated with the development of oral lesions. Consequently, the lesions found in patients with a diagnosis of COVID-19 may be more related to drugs or the immunosuppression induced by the treatment of COVID-19 (21, 22). In addition, Guo *et al.* (26) comments that, in the fight against COVID-19, psychological stress associated with fear, doubts and uncertainties about the disease definitely becomes the main factor inducing the development of lesions in the oral mucosa not only in patients with COVID-19 but in the general population.

Lastly, Petrescu *et al.* (27) and Martin Carreras-Presas (28) emphasizes the careful intraoral examination of the mucosa in suspect patients infected by SARS-CoV-2. Thorough research is needed to understand the connection between oral mucosal lesions and COVID-19.

## DISCUSSION

This review identified scientific publications on the manifestation of oral lesions in patients with COVID-19 amid the global pandemic which already exceeds 22 million diagnosed cases (29). It was noted that the studies published since the first case of infection with SARS-CoV-2 reported common signs and symptoms in patients infected with this virus, such as fever, headache, myalgia, fatigue, cough, sputum production, sore throat, diarrhea, and dyspnea (3, 14). The repercussion of the work published by Martin Carreras-Presas *et al.* (8) regarding the presence of lesions in the oral mucosa of COVID-19 patients and the suggested association with the disease aroused the interest of the dental community. The identification of lesions at different

times during the course of the disease and reports suggesting that these lesions may be the first sign of the disease have prompted investigations (18).

Cutaneous manifestations have been described since the discovery of the virus since they are visible and are therefore more likely to be identified (12, 13, 16). In contrast, the oral cavity is not commonly evaluated and there are only few reports of small groups of patients with oral manifestations (8, 10). Thus, all health professionals, especially doctors and dentists, should be encouraged and instructed to perform intraoral examinations in patients with a suspicion or diagnosis of COVID-19, always following biosafety guidelines in order to identify possible oral lesions that may be directly or indirectly associated with the disease (8, 20).

Some of the oral manifestations identified in patients with COVID-19 include ulcerations, desquamative gingivitis, gingival bleeding, enanthem, plaques, inflammation of the lingual papillae, papules, and vesiculobullous lesions, which comprise a range of common lesions (11, 15, 18, 26) and thus resemble other viral diseases with oral manifestations (21, 24, 25). Viral infections are generally characterized by a sudden onset associated with enanths, ulcerations or blisters. Thus, caution is needed when associating these clinical signs with COVID-19 since there are many viruses that can affect the oral cavity and cause these lesions (30). The differential diagnosis with numerous other diseases that manifest in the oral mucosa and have nonspecific symptoms is important. These diseases include chikungunya, dengue, zika, measles, mononucleosis, herpangina, hand-foot-and-mouth disease, herpes zoster, and herpes simplex type 1 (HSV-1) (31-35).

The most common lesions in the oral cavity triggered by viral diseases are HSV-1, herpes zoster, and mononucleosis, all of them belonging to the herpes virus family. Several cases with lesions similar to those seen during the recurrence of HSV-1 have been reported. Although the lesions were associated with COVID-19, in some cases the diagnosis of the disease was not confirmed (8, 9, 17). Thus, inferring that the lesions of these suspected patients are derived from COVID-19, although without confirmation and without other associated signs or symptoms, may be premature.

Herpes zoster lesions also resemble those reported in the studies and should be included in the differential diagnosis with lesions observed in patients with COVID-19. In the medical field, dermatologists already reported evidence of reactivation of HSV-1 and cases of herpes zoster in patients with COVID-19 (36, 37). It must therefore

be emphasized that dealing with this new virus whose characteristics sometimes resemble those of other viral diseases that have been present for some time requires attention, including the need for complementary tests that support the diagnosis and exclude other diseases.

Amid the pandemic, social isolation, unemployment and uncertainties, it is not unlikely that many people were or are still anxious and have doubts about the future and regarding recovery when affected by the disease, and consequently develop immune-related lesions. In addition, the multidrug treatments applied accelerate and stimulate the development of lesions such as erythema multiforme which, when associated with COVID-19, is widely called erythema multiforme-like and has been diagnosed in patients undergoing more intensified drug therapy (12, 38).

Some of the published reports were contested since there is still not sufficient evidence to confirm the action of SARS-CoV-2 on the mucosa. Current studies shows that ACE2-expressing cells may act as target cells for the SARS-COV-2 such and the ACE2 receptor is highly enriched in epithelial cells

of oral mucosal (39) which could have a direct effect on the mucosa. Therefore, the scientific literature is taking its first steps in understanding the impact of the pathogenesis of SARS-CoV-2 on the oral cavity. Further research is needed to confirm whether oral lesions are related to COVID-19 or whether they are secondary manifestations resulting from suppression of the immune system and stress caused by the pandemic.

## CONCLUSION

The etiology of many oral mucosal lesions is intimately related to infectious, immunological, and psychosocial factors. Therefore, amid the SARS-CoV-2 pandemic in which many doubts about the disease still remain, caution is needed when evaluating patients and establishing correlations with other diseases that could be associated.

## CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest in relation to this study.

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