



Oral and maxillofacial complications of COVID-19 infection: A review

Farzaneh Bolandparva ^{1*}, Mona Mohajeri Tehrani ², Najmeh Heydari ³

1. Department of Oral and Maxillofacial Surgery, School of Dentistry, Tehran University of Medical Sciences, Tehran, Iran.

2. Craniomaxillofacial Research Center, Tehran University of Medical Sciences, Tehran, Iran.

3. School of Dentistry, Tehran University of Medical Sciences, Tehran, Iran.

ARTICLE INFO

Article Type:
Review Article

Received: 10 Jun. 2023

Revised: 2 Jul. 2023

Accepted: 1 Aug. 2023

*Corresponding author:

Farzaneh Bolandparva

Department Oral and Maxillofacial Surgery, School of Dentistry, Tehran University of Medical Sciences, Tehran, Iran.

Tel: +98-912-7642154

Fax: +98-21-84902473

Email: f.bolandparva@gmail.com

ABSTRACT

Introduction: The SARS-CoV-2 virus is a group of viruses that cause disease in birds and mammals and currently has more than 398,572,320 infected and 5,770,578 victims worldwide. Common clinical symptoms are fever, headache, dyspnea, sore throat, dry cough, abdominal pain, diarrhea, and nausea. On the other hand, the results of various studies related to oral and maxillofacial manifestations in patients with COVID-19 have reported contradictory results in different places, which shows the role of different geographical and individual factors in the occurrence of oral manifestations. The aim of the present study was to review the oral and maxillofacial manifestations in patients with or improved COVID-19 infection.

Materials and Methods: This study is a narrative review. In this study, research published in Pubmed, Google Scholar and Scopus databases has been reviewed by a review method and with a keyword search strategy.

Results: 4011 articles were found from the mentioned databases, and after deleting unrelated researches (3607 cases) and duplicate researches (358 cases), 46 articles remained for final review. Then, from this number, those research that were presented in the scientific conference and were in the form of abstracts or did not have a correct statistical population were excluded from the study (10 cases).

Conclusion: COVID-19 is a new and rapidly evolving disease, and many of its features, including its associated oral manifestations, are still under investigation. No agreement has yet been reached on the nature and classification of oral lesions in COVID-19 and their causal relationship to disease progression. This limitation is reflected in systematic reviews such as the present article. In addition, there is a significant shortage of high-quality studies on the prevalence of these oral manifestations and this limitation affects the prevalence estimates presented in this study.

Keywords: Oral manifestations; Maxillofacial manifestations; Sars covid_19.

Introduction

Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus that causes disease in birds and mammals [1]. Bats are believed to be its primary reservoir and the virus could pass to an intermediate host, possibly an anteater or other animals. Transmission to humans could have occurred through the sale of these animals in the Wuhan market. Subsequently, human-to-human transmission occurred

mainly via aerosols [2]. COVID-19 is presumably transmitted by droplets, close contact, aerosols, and possibly oral and fecal transmission even during the incubation period [3,4]. Expression of ACE2 as the major COVID-19 receptor is widespread in the upper part of the esophagus, in epithelial cells, and in absorptive enterocytes of the ileum and colon, suggesting that the orofecal route may be a possible route of transmission in addition to the respip-

ratory tract [39-40]. However, some studies claim that the risk of virus transmission through the feces of an infected person is low [5]. The spike surface glycoprotein (S) of coronaviruses plays an essential role in binding the virus to the cell surface receptor. Previous studies have shown that SARS viruses enter the cell via the ACE-2 (angiotensin-converting enzyme-2) receptor [6]. Glycoproteins presented in the capsid of SARS and MERS can provoke an event called a cytokine storm, which is a potential cause of death in involved subjects. The virus enters the body through mucous membranes such as the nose and throat and attacks organs such as the lungs, heart, kidneys, and gastrointestinal system, where enzymes such as ACE-2 are present [7]. Asymptomatic carriers are crucial in the spread of the disease. Information on asymptomatic carriers is limited. Many carriers of this disease are under 15 years of age and show no symptoms. Real-time PCR is the best method for diagnosis, as a lung CT scan is not indicative in these cases [8]. Most expired patients are elderly men with an average age of 75 who have a history of diseases such as diabetes, hypertension, cardiovascular disease, chronic respiratory disease, and cancer, or a history of previous surgery. Well-functioning immune system is the most important component against viral infections, which is weakened in the elderly. Immuno-related genes on the X-chromosome and sex hormones that affect innate and acquired immune responses, may account for the predisposition of males over females to this infection [9,10].

At the time when this article was being carried out, there were over 398,572,320 confirmed cases and 5,770,578 deaths worldwide [11,12]. Common clinical symptoms include fever, headache, shortness of breath, sore throat, dry cough, abdominal pain, diarrhea, and nausea [13]. The infection affects various organs such as the liver, kidneys, lungs, digestive system, and even the epithelium of the salivary glands. The involvement of the respiratory tract leads to rapid spread of the virus, affecting multiple organs and eventually death of the patient [14]. The typical incubation period is about 3 days (with a range of 0 to 24 days), and the average duration from the appearance of first symptoms to death is 14 days [5]. The duration of the commune period of COVID-19 varies widely and is averagely higher than that of SARS. (15) In 5% of cases, patient's condition worsens with respiratory failure, infectious shock, and failure of other organs [16]. SARS digestive symptoms such as diarrhea are rarely seen in patients with Coronavirus SARS-CoV-2 [17,18]. External pulmonary manifestations are Olfactory disorder, Ageu-

sia, Gastrointestinal disease, Cardiovascular disease, kidney and liver disease, skin manifestation, Cerebrovascular accident and diabetes complications. Loss of sense of smell in adults after infection with infectious upper respiratory tract viruses is called "anosmia following viral infection", which accounts for about 40 percent of cases of anosmia [19]. Theoretically, viruses can also pass through the cribriform plate of the ethmoid bone to the olfactory bulb, which is one of the lower structures of the brain that processes olfactory information. Infiltration of viruses could lead to damage of this nerve area and eventually to olfactory dysfunction [20]. Ageusia is a Lack of sense of taste is mainly secondary to olfactory dysfunction [19]. Common gastrointestinal symptoms such as diarrhea, nausea and vomiting have been reported [21]. One of the rare symptoms reported in Covid-19 patients is "skin rash", in the form of erythematous, widespread hives and chickenpox-like blisters (with or without itching) on the trunk of the body.

Myocarditis and cardiac arrest have been mentioned in other published reports. The most common mechanisms responsible for this damage may be direct injury to myocardial cells by 2-CoV SARS or immune-mediated inflammation (cytokine storm) or as a result of hypoxemia [22,23]. CT scans have also indicated decreased renal density, inflammation, and edema in certain individuals. Recently, hematuria and high serum creatinine levels have been reported in COVID-19 patients [24]. Abnormal levels of AST and ALT are usually transient and often resolve with regression of the disease but in severely infected patients, damages can be more extensive [25]. Moreover, Diabetes complication serves as a two-bladed sword as diabetes increases vulnerability of individuals to coronavirus infection, on the other hand, COVID-19 patients become more susceptible to ketoacidosis shock and other similar complications; even healthy people can become diabetic, after corona-virus infection [26]. Hypercoagulation, viral neurotropism, hypoxia, endothelial dysfunction and inflammation could all potentially contribute to the development of CVA [27]. It has recently been found that saliva sampling by reverse transcriptase chain reaction (RT-PCR) may even be a more sensitive test than the nasopharyngeal test. ACE-2 (Angiotensin-converting enzyme 2) receptors are found in the oral mucosa with higher density in the posterior of the tongue, palate and buccal mucosa. Therefore, due to the high concentration of this enzyme and viral DNA in the oral mucosa, patients with this infection can be expected to have oral manifestations [13,14,28]. The re-

sults of various studies have shown that the proteins of the virus are present in saliva and mucosal epithelium even after symptoms have resolved. Accordingly, we can use oral manifestations as predictive factors for the persistence of viral particles in the body and the possibility of disease recurrence [29,30]. In various studies, several cases of oral manifestations such as dry mouth, taste disturbance, Candidiasis, and geographic tongue have been reported in patients with COVID-19 [29,31-33]. Therefore, it holds significance to carry out research to comprehend how often and for how long oral symptoms occur in individuals who have recovered from and those who are currently affected by the condition. Dentists play a critical role in the early diagnosis of COVID-19 and they can prevent transmission of the disease within the dental team. Also, dentists; role as members of a multidisciplinary team that monitors COVID-19 patients in the ICU is undeniable because oral lesions can have a notable impact on how the disease develops or how medication side effects manifest themselves. several studies of oral and maxillofacial manifestations in COVID-19 patients in different locations have shown conflicting results, indicating the influence of geographic and individual factors. To better understand these variations this review study seeks to examine how common oral and facial symptoms are, among patients who have contracted the COVID-19 virus based on age, sex, duration of infection, length of hospital stay and need for intubation [34].

Materials and Methods

This review was conducted by searching the follow-

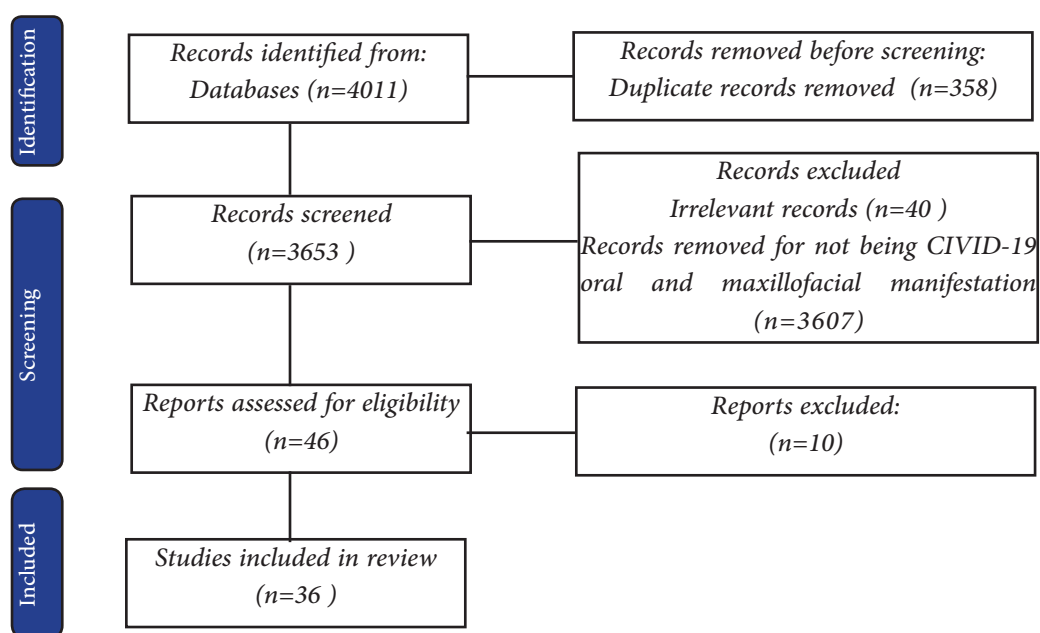


Figure 1. Identification of studies via databases (flowchart of conducted study).

ing keywords “oral manifestation, maxillofacial manifestations, covid-1, SARS-CoV-19, mucormycosis” in PubMed, SCOPUS, ISI Web of Science, Cochrane, Google Scholar, and SID websites between December 2019 and December 2021 to obtain all studies in English. This review used a set of inclusion and exclusion criteria to enter studies in the field. The inclusion criteria were RCTs, prospective and retrospective studies only in English that had accessible full text and eligible control groups. Non-English articles, non-related articles, repetitive articles, articles without full text, and low-quality studies such as doctoral theses, expert opinions, letters, and editorials were excluded. Thus, after duplication elimination, the researcher assessed the title, abstract, and full text of the studies based on inclusion criteria. Then, the included articles were evaluated based on scientific principles and methodological accuracy. Their references were reviewed manually. Additionally, related articles were evaluated and included in this study if they met the specified conditions. Subsequently, we register the following information: citation (author/year), article title, type of study, sample size, frequency of oral and maxillofacial manifestations, duration of hospitalization, duration of infection, need for intubation, treatment method, and duration of follow-up. After collecting information from various sources, the results were classified in the form of charts and the tables and the contents were integrated, giving more weight to the stronger sources. To increase the accuracy, all articles were read by the same person to avoid inter-individual differences. Figure 1.

Results

Using the described search strategy, a total of 4011 publications were retrieved. After removing duplicate articles, the total number was reduced to 3653. These 3653 publications were subjected to title and abstract

screening. 3607 studies were excluded that had less or no relation to oral or maxillofacial manifestations of COVID-19. 10 publications were excluded based on the inclusion criteria. A total of 36 publications were selected for full-text screening. Table 1.

Table 1. COVID-related oral manifestations in published works.

Study	Author	Type of study	Year of publication	Journal	Correspondence country	Oral manifestation	Maxillofacial manifestation	Age	Sex	Period of hospitalization	Period of infection	Need for intubation	Treatment	Follow up intervals	Lesion type	Sample	Results	
Literature review	Natalia Sandoval-Gómez	Literature review	2021	Odon-tomes-tomato-logia	Chile	Dry mouth, burning sensation, ulcer, desqua-mative gingivi-tis, ery-thema, salivary gland infection	Not men-tioned	Not men-tioned	Not men-tioned	Not men-tioned	Not men-tioned	Not men-tioned	Not men-tioned	Not men-tioned	Not men-tioned	Herpeti-form lesion, geo-graphic tongue, pustula, pete-chiae, blister	47 arti-cles	Common oral man-ifestations of the covid - 19 are taste disor-ders, mouth dryness, ulcers, vesicles and etc.
Case report	Eliete Neves Silva Guerra	Original	2020	Interna-tional Journal of In-fectious Disease	Brazil	taste decrease	Not men-tioned	67	male	44 days	54 days	Not men-tioned	IV Flu-conazole, oral Nystatin, non-al-coholic chlor-hexidine diglu-conate (0.12%)	10 days	Geo-graphic tongue, nodule, recurrent herpes simplex-virus	1	The oral conditions confirm that lesions' Severity is Secondary to worsen-ing systemic health or covid-19 treatments	
Observational study	Bruna Sinjari	Original	2020	Journal of Clinical Medicine	Italy	Dry mouth, dysgeu-sia*, burning sensation, swal-lowing dysfunction		On average: 69.2	55% male; 45% female	Not men-tioned	Not men-tioned	Not men-tioned	Lopina-vir/ri-tonavir/hydroxy-chloro-quine			20 pa-tients	The need for further studies to fully understand the effects of Covid-19 on patients is undeni-able. The preva-lence of dry mouth in hospitalized patients increases signifi-cantly with increasing length of hospital stay. Oral hygiene also decreased significantly with with increasing duration of hospital-ization.	

Study	Author	Type of study	Year of publication	Journal	Correspondence country	Oral manifestation	Maxillofacial manifestation	Age	Sex	Period of hospitalization	Period of infection	Need for intubation	Treatment	Follow up intervals	Lesion type	Sample	Results
Population-based cross-sectional study	Ghalehbaghi	Original	2020	Med J Islamic Republic of Iran	Iran	dysgeusia*	Hyposmia†, Anosmia ‡(olfactory dysfunction)	7-78		both	Not mentioned	More than 30 days	Not mentioned	Not mentioned	Not mentioned	10069	Sudden onset of olfactory dysfunction in 76.24%, continuous anosmia in 60.90%, and simultaneous olfactory and gustatory disturbances in 80.38% of the Participants was reported
Case series	Tamer Roushdy	Original	2021	The Egyptian Journal of Neurology, Psychiatry and Neurosurgery	Egypt	Cutaneous mucormycosis		59/80/73/59 Female, male, male		2w, 4w, 2w, not mentioned	5w, 4w, not mentioned, not mentioned	not mentioned	not mentioned, broad spectrum antibiotic and systemic amphotericin B, systemic and local ophthalmic antibiotic, liposomal systemic amphotericin B, systemic Amikacin and amphotericin B	not mentioned, loose wound of hard palate, polypoid lesion, blackish discoloration of hard palate	4	Today, we should consider the rare but deadly fungal infection especially in COVID patients who have concomitant systemic diseases such as uncontrolled diabetes or who are treated with high doses of corticosteroids	
Review	Ritesh Agarwal	Review	2021	Mycopathologia	India	mucormycosis		Not mentioned	Both	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	2568	the mortality rate reported in India (36.5%) was lower than the cases reported worldwide (61.9%) Probably due to being overwhelmed by the rhino-orbital mucormycosis

Study	Author	Type of study	Year of publication	Journal	Correspondence country	Oral manifestation	Maxillofacial manifestation	Age	Sex	Period of hospitalization	Period of infection	Need for intubation	Treatment	Follow up intervals	Lesion type	Sample	Results
Systematic review	Ana Suárez	Systematic and meta analysis	2021	Frontiers in Medicine	Spain	Dry mouth		18-77	Both	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Aphthous, salivary gland involvement	74 studies	33% Oral lesions 44% dry mouth 23% aphthous lesions
Review	Huma Farid	Review	2021	Wiley	Pakistan	Dry mouth, dysgusia			Both	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	outbreak of HSV-1, geographic or fissured tongue, gingivitis, ulcer, plaque type lesions, petechiae	19 studies	Dental specialists may encounter with Covid 19 patients and are asked to identify various oral manifestations of this disease.
Brief review	Sadeq Ali MAW-ERI	Review	2020	Critical review oral pathology	Qatar		Not mentioned	6-77	61.1% female	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Ulcerative lesions, vesiculobullous lesions, macula, parotiditis	25 studies	Oral examination of all suspected and confirmed COVID -19 is essential for better understanding and documentation. (Oral manifestations were the first signs of COVID in four patients)
Case series	Awadhesh Kumar Singh	Original	2021	Diabetes & Metabolic Syndrome: Clinical Research & Reviews	India		Rhino-orbital mucormycosis	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Corticosteroids	Not mentioned	Not mentioned	101 patients, 28 studies	it looks like diabetes, excessive use of corticosteroids in COVID -19 patients may Promote mucormycosis, so clinicians should maintain optimal glucose intake and use corticosteroids judiciously in aforementioned Patients

Study	Author	Type of study	Year of publication	Journal	Correspondence country	Oral manifestation	Maxillofacial manifestation	Age	Sex	Period of hospitalization	Period of infection	Need for intubation	Treatment	Follow up intervals	Lesion type	Sample	Results
Casereport	Sai Krishna	Original	2021	Indian J Otolaryngol Head Neck Surg	India		Invasive osteolytic lesions with maxillary tendency, swelling on the right side and midface	34/50	Male/male	Not mentioned	2 months	Not mentioned	IV liposomal amphotericin B, insulin	Not mentioned	Osteomyelitis, mucormycosis	2 patients	Surgery was immediately performed on both patients.
Observational	Dina M. El Kady	Original	2021	Clinical and experimental dental research	Egypt	dysgeusia*, dry mouth, tongue erythema, loss of senses	Anosmia ‡	18-46	53.4% males and 46.6% females	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned		58	Based on limited data, COVID-19 has significant effects on the oral cavity and salivary glands, so symptoms related to the glands. Salivation and taste disorders in COVID-19 patients is very common.
Review	Gianrico Spagnuolo	Review	2021	International Journal of Environmental Research and Public Health	Russia	dysgeusia*	Anosmia ‡	40-45	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Geographic tongue, fibroma, outbreak of herpes virus	875 studies	Long term symptoms after COVID-19 can take over. Providing dental treatment needed to affect.
Case-control	Nadya Tamimi	Original	2021	Journal of Clinical Periodontology	Qatar	peri-odontitis		18-40		Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Periodontal lesions	568 patients	Higher risk of peri-odontitis, hospitalization in intensive care unit, need for assisted ventilation and patient death. COVID-19 and rising levels of biomarkers in blood associated with poorer outcomes.

Study	Author	Type of study	Year of publication	Journal	Correspondence country	Oral manifestation	Maxillofacial manifestation	Age	Sex	Period of hospitalization	Period of infection	Need for intubation	Treatment	Follow up intervals	Lesion type	Sample	Results
Review	Dilnoza T. Bobamuratova	Review	2021	Advances in Oral and Maxillofacial Surgery	Uzbekistan		Maxillary and facial bones necrosis, ocular and neural complications	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	179	serious facial complication due to COVID-19 or its treatment.
Review	Behzad Iranmanesh	Review	2020	Dermatologic Therapy	Iran	dysgeusia*		Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Varicose lesions, erythema multiform (EM), hives, maculopapular, petechiae and purpura, Spotty lesions, pseudoreticular lesions, aphthous stomatitis, herpetic form lesions, white and red plaques	35 studies	Oral lesions were almost equally common in both sexes (49%) women (51%). Patients with older age or more severe Covid-19 show more extensive oral lesions.
Systematic review	E.N.S. Guerra	Review	2021	Journal of Dental Research	Brazil	dysgeusia*, hypogeusia, ageusia		Not mentioned	4288 men, 5770 women and 170 anonymous	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Geographic and fissured tongue, mucosal lesions (red and white plaque, yellowish ulcers)	35 studies, 10228 patients, 40 studies	Possible taste disturbances are one of the first manifestations of COVID-19 patients and must be considered in the onset and progression of the disease

† decreased sense of smell.

‡ partial or full loss of smell.

* a condition in which a foul, salty, rancid, or metallic taste sensation persists in the mouth.

Discussion

In this study, we reviewed oral and maxillofacial complications caused by Covid 19 disease. Originally, olfactory and gustatory disturbances associated with COVID-19 were possible indications of SARS-CoV-2 infection and were sometimes even described as the only symptom of the disease [35]. In 2020, Bidasee et al conducted a study of 70 men and 70 women to assess the frequency of oral and olfactory manifestations in patients with COVID-19 infection by sex. Oral and olfactory disturbances and facial and neck pain were queried. Common symptoms were headache, olfactory and gustatory disturbances, rhinorrhea, and nasal congestion. The prevalence of rhinorrhea and headache was significantly higher in women [30]. In some isolated cases, mouth sores, red spots (mainly on the palate; in addition to the gums), and mucosal vesicles on the lower lip and cheeks were reported [31,36-38]. Soares et al (2020) reported aphthous lesions, and numerous red spots on the tongue, palate, and buccal mucosa that recovered within 3 weeks [39]. COVID-19 can affect the ability to taste by interfering with the ACE2 receptors in the taste bud cells [40].

In a study by Dos Santos et al oral manifestations in patients with Covid-19 infection were reviewed. In 10228 patients from 19 countries, the most common intraoral manifestation was taste disturbance, with a prevalence of 45%, most of which was related to changes in the sense of taste rather than its complete loss. The prevalence of taste disorders was higher in women than in men ($p=0.0007$) [41]. Women show a higher tendency for taste impairment, which is the most common manifestation of the oral cavity [42]. Taste disorders have symptoms that are easy to recognize and serve as early warning signs so that COVID-19 can be detected immediately. This may directly help to curb the rapid spread of the disease, especially in countries where testing capacity has declined [43]. COVID-19 Patients may have taste disturbances even in the absence of olfactory problems, as taste disturbances are often more common. The virus affects the peripheral nervous system, which follows disorders in taste buds as they are peripheral nerve endings. SARS-CoV-2 could also intercept some components of salivary mucus such as salicylic acid, leading to taste conditions. In addition, the high expression of ACE2 in the tongue suggests a potential pathway. ACE Inhibitors and ACE2 blockers, commonly used drugs, are also associated with taste disorders due to their effect on G-proteins and sodium-channel inactivation [44]. Other symptoms such as ulcers and blisters on the lower lip and cheek (like

herpetic ulcers), gingivitis, petechiae (mainly in the palate), geographic tongue and concurrent infections such as candidiasis were seen in these patients but It is unclear whether the symptoms are caused by direct infection with SARS-CoV-2 or a systemic consequence of possible infection due to prolonged hospitalization, a weakened immune system, and adverse drug treatment [45-48]. In the 2021 study by Sufi Mahmoudi, the oral manifestations of COVID-19 patients were independently reviewed by two reviewers. Seventeen studies reported 226 confirmed cases. The age range was 9 to 90 years. The most common oral manifestations were dry mouth (75 subjects), dysgeusia (71 subjects) and pseudomembranous fungus (67 subjects), changes in tongue sensation (48 subjects) and gastric ulcers (28 subjects), muscle pain on chewing (15 subjects), swelling in the oral cavity (10 subjects), and herpes lesions (6 subjects). The mean time of onset of oral manifestations was 7.21 days after systemic symptoms (range: 10-42). In 42 cases, the oral lesions healed spontaneously or with initial treatment within three weeks (105) White and red lesions were most common on the tongue, buccal mucosa, palate, and lower lip appearing 7 to 24 days after hospitalization [41]. Bodard et al, in a 2020 case report study, reported a case complaining of pain and swelling on the dorsal surface of the tongue. Thus, the initial diagnosis was multiple papules on the dorsal surface of the tongue and around the salivary glands. After examining the patient's systemic symptoms and diagnosing fever and respiratory illness in follow-up sessions, a diagnosis of covid 19 infection was made based on serologic testing and chest radiographs [34].

Painful necrotic ulcers and extensive aphthous lesions have been reported in some studies [39,49]. Moreover, fungal infections, mainly caused by the aspergillosis fungus, have been shown to cause osteomyelitis of the maxilla. In addition, the development of osteonecrosis of the jaw by certain drugs used in the treatment of rheumatoid arthritis (such as tocilizumab), systemic suppressors, bisphosphonates, other antiallergic drugs, a number of drugs categorized as tyrosine kinase inhibitors, monoclonal antibodies, radiopharmaceuticals, and selective estrogen receptor modulators has been implicated in osteonecrosis of the jaw. considering rheumatic treatment of patients with severe COVID-19 due to high CRP, osteonecrosis of the jaw may be observed in the aforementioned patients [50,51].

Oral hygiene may also serve as a good indicator for evaluating the relationship between COVID-19 infection and the occurrence of oral manifestations. Badran et al. hypothesized that periodontal pockets may be a source of this virus [48]. The involvement of the salivary glands and palatal mucosa in COVID-19 may result in various oral manifestations such as dry mouth, burning tongue, and impaired function. These symptoms may persist even after other COVID-19 symptoms resolve. Although the main symptoms of COVID-19 are respiratory symptoms, blood clotting disorders such as Thrombosis and thromboembolism are common findings. Cavernous sinus thrombosis is a very rare condition and it is life-threatening. It is usually caused by an infection originating in the sinuses, teeth, throat, ears, or eyes, or by trauma [49].

Many oral lesions observed in COVID-19 patients are not directly caused by the infection and therefore should not be classified as oral manifestations of the disease. An important group in this category is iatrogenic lesions caused by long-term intubation and invasive methods [52,53]. Drug reactions in the form of lesions can also be included in this category [54]. Another group of oral lesions that occur in patients with COVID-19 but are not directly attributable to the pathologic processes of SARS-CoV-2 infection are opportunistic coinfections, such as candidiasis and herpes simplex infections, which usually occur in debilitating diseases [55-59]. Dos Santos et al. reported a case study in 2020 of a 68-year-old patient who underwent RT-PCR testing. Intraoral examination of this patient revealed concurrent infection with geographic tongue, oral candidiasis, and recurrent herpetic ulcers, which was due to the weakness of the immune system [31].

The treatment prognosis of COVID-19 patients also depends on the extent of their oral and maxillo-facial manifestations, as treatment is usually associated with suppression of the host immune system and this could potentially provoke oral reactions due to immunosuppression such as mucormycosis, candidiasis, and herpes labialis [29,60]. Therefore, we see a number of oral manifestations in patients undergoing treatment. The present study has certain limitations. Because COVID-19 is a new and rapidly evolving disease, many of its features, such as the oral manifestations and the association between them and the pathologic process of the disease, remain largely unexplored. The classification of oral lesions in COVID-19 is still in limbo. moreover, there is a great lack of high-quality studies in this area, so we need more research such as clinical trials and observational studies on the oral effects of

COVID-19 and their impact on the overall health of patients.

Conflict of Interest

There is no conflict of interest to declare.

References

- [1] Ludwig S, Zarbock A. Coronaviruses and SARS-CoV-2: A Brief Overview. *Anesth Analg.* 2020; 131(1):93-6.
- [2] Li X, Zai J, Zhao Q, Nie Q, Li Y, Foley BT, Chailion A. Evolutionary history, potential intermediate animal host, and cross-species analyses of SARS-CoV-2. *Journal of medical virology.* 2020; 92(6):602-11.
- [3] Wu F, Zhao S, Yu B, Chen Y-M, Wang W, Song Z-G, et al. A new coronavirus associated with human respiratory disease in China. *Nature.* 2020; 579(7798):265-9.
- [4] Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *nature.* 2020; 579(7798):270-3.
- [5] Sun J, He W-T, Wang L, Lai A, Ji X, Zhai X, et al. COVID-19: epidemiology, evolution, and cross-disciplinary perspectives. *Trends in molecular medicine.* 2020; 26(5):483-95.
- [6] Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh C-L, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science.* 2020; 367(6483):1260-3.
- [7] Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. *Nature microbiology.* 2020; 5(4):562-9.
- [8] Organization WH. Water, sanitation, hygiene, and waste management for the COVID-19 virus: interim guidance, 19 March 2020. World Health Organization; 2020.
- [9] Jaillon S, Berthenet K, Garlanda C. Sexual dimorphism in innate immunity. *Clinical reviews in allergy & immunology.* 2019; 56:308-21.
- [10] Libert C, Dejager L, Pinheiro I. The X chromosome in immune functions: when a chromosome makes the difference. *Nature Reviews Immunology.*

- gy. 2010; 10(8):594-604.
- [11] Chung JY, Thone MN, Kwon YJ. COVID-19 vaccines: The status and perspectives in delivery points of view. *Advanced drug delivery reviews*. 2021; 170:1-25.
- [12] Halboub E, Al-Maweri SA, Alanazi RH, Qaid NM, Abdulrab S. Orofacial manifestations of COVID-19: a brief review of the published literature. *Brazilian oral research*. 2020; 34.
- [13] Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, et al. Clinical characteristics of coronavirus disease 2019 in China. *New England journal of medicine*. 2020; 382(18):1708-20.
- [14] Hedou M, Carsuzaa F, Chary E, Hainaut E, Caze-nave-Roblot F, Regnault MM. Comment on 'Cutaneous manifestations in COVID-19: a first perspective' by Recalcati S. *Journal of the European Academy of Dermatology and Venereology*. 2020; 34(7):e299.
- [15] Yang Y, Lu Q-B, Liu M-J, Wang Y-X, Zhang A-R, Jalali N, et al. Epidemiological and clinical features of the 2019 novel coronavirus outbreak in China. *medrxiv*. 2020:2020.02. 10.20021675.
- [16] Zu ZY, Jiang MD, Xu PP, Chen W, Ni QQ, Lu GM, Zhang LJ. Coronavirus disease 2019 (COVID-19): a perspective from China. *Radiology*. 2020; 296(2):E15-E25.
- [17] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020; 395(10223):507-13.
- [18] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The lancet*. 2020; 395(10223):497-506.
- [19] Machado C, Gutierrez JV. Anosmia and ageusia as initial or unique symptoms after sars-cov-2 virus infection. 2020.
- [20] Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. *ACS chemical neuroscience*. 2020; 11(7):995-8.
- [21] Wang L, Gao Y-h, Lou L-L, Zhang G-J. The clinical dynamics of 18 cases of COVID-19 outside of Wuhan, China. *European Respiratory Journal*. 2020; 55(4).
- [22] Bansal M. Cardiovascular disease and COVID-19. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*. 2020; 14(3):247-50.
- [23] Tan W, Aboulhosn J. The cardiovascular burden of coronavirus disease 2019 (COVID-19) with a focus on congenital heart disease. *International journal of cardiology*. 2020; 309:70-7.
- [24] Li Z, Wu M, Yao J, Guo J, Liao X, Song S, et al. Caution on Kidney Dysfunctions of 2019-nCoV Patients (preprint). 2020.
- [25] Zhang C, Shi L, Wang F-S. Liver injury in COVID-19: management and challenges. *The lancet Gastroenterology & hepatology*. 2020; 5(5):428-30.
- [26] Chee YJ, Ng SJH, Yeoh E. Reply to comments on Letter to the Editor-Diabetic ketoacidosis precipitated by Covid-19 in a patient with newly diagnosed diabetes mellitus. *diabetes research and clinical practice*. 2020; 166:108305.
- [27] Reddy ST, Garg T, Shah C, Nascimento FA, Imran R, Kan P, et al. Cerebrovascular disease in patients with COVID-19: a review of the literature and case series. *Case reports in neurology*. 2020; 12(2):199-209.
- [28] Seirafianpour F, Sodagar S, Pour Mohammad A, Panahi P, Mozafarpour S, Almasi S, Goodarzi A. Cutaneous manifestations and considerations in COVID-19 pandemic: a systematic review. *Dermatologic therapy*. 2020; 33(6):e13986.
- [29] Amorim Dos Santos J, Normando AGC, Carvalho da Silva R, Acevedo AC, De Luca Canto G, Sugaya N, et al. Oral manifestations in patients with COVID-19: a living systematic review. *Journal of dental research*. 2021; 100(2):141-54.
- [30] Biadsee A, Biadsee A, Kassem F, Dagan O, Masarwa S, Ormianer Z. <? covid19?> Olfactory and Oral Manifestations of COVID-19: sex-related symptoms—a potential pathway to early diagnosis. *Otolaryngology-Head and Neck Surgery*. 2020; 163(4):722-8.
- [31] Dos Santos JA, Normando AGC, da Silva RLC, De Paula RM, Cembranel AC, Santos-Silva AR, Guerra ENS. Oral mucosal lesions in a COVID-19 patient: new signs or secondary manifestations?

- International Journal of Infectious Diseases. 2020; 97:326-8.
- [32] Iranmanesh B, Khalili M, Amiri R, Zartab H, Afatoonian M. Oral manifestations of COVID-19 disease: A review article. *Dermatologic therapy*. 2021; 34(1):e14578.
- [33] Tanner MC, Boxriker S, Haubruck P, Child C, Westhauser F, Fischer C, et al. Expression of VEGF in Peripheral Serum Is a Possible Prognostic Factor in Bone-Regeneration via Masquelet-Technique—A Pilot Study. *Journal of Clinical Medicine*. 2021; 10(4):776.
- [34] Chaux-Bodard A-G, Deneuve S, Desoutter A. Oral manifestation of Covid-19 as an inaugural symptom? *Journal of Oral Medicine and Oral Surgery*. 2020; 26(2):18.
- [35] Sofi-Mahmudi A. Patients with COVID-19 may present some oral manifestations. *Evid Based Dent*. 2021; 22(2):80-1.
- [36] Martín Carreras-Presas C, Amaro Sánchez J, López-Sánchez AF, Jané-Salas E, Somacarrera Pérez ML. Oral vesiculobullous lesions associated with SARS-CoV-2 infection. *Oral Dis*. 2021; 27 Suppl 3(Suppl 3):710-2.
- [37] Rocha BA, Souto GR, Grossmann SMC, de Aguiar MCF, de Andrade BAB, Romañach MJ, Horta MCR. Viral enanthema in oral mucosa: A possible diagnostic challenge in the COVID-19 pandemic. *Oral Dis*. 2021; 27 Suppl 3(Suppl 3):776-8.
- [38] Tong JY, Wong A, Zhu D, Fastenberg JH, Tham T. The Prevalence of Olfactory and Gustatory Dysfunction in COVID-19 Patients: A Systematic Review and Meta-analysis. *Otolaryngol Head Neck Surg*. 2020; 163(1):3-11.
- [39] Soares CD, Carvalho RA, Carvalho KA, Carvalho MG, Almeida OP. Letter to Editor: Oral lesions in a patient with Covid-19. *Med Oral Patol Oral Cir Bucal*. 2020; 25(4):e563-e4.
- [40] Cai G. Bulk and single-cell transcriptomics identify tobacco-use disparity in lung gene expression of ACE2, the receptor of 2019-nCov. *MedRxiv*. 2020:2020.02. 05.20020107.
- [41] Amorim dos Santos J, Normando AGC, Carvalho da Silva RL, Acevedo AC, De Luca Canto G, Sugaya N, et al. Oral Manifestations in Patients with COVID-19: A 6-Month Update. *Journal of Dental Research*. 2021; 100(12):1321-9.
- [42] Maheswaran T, Abikshyeet P, Sitra G, Gokulnathan S, Vaithyanadane V, Jeelani S. Gustatory dysfunction. *Journal of pharmacy & bioallied sciences*. 2014; 6(Suppl 1):S30.
- [43] Prather KA, Wang CC, Schooley RT. Reducing transmission of SARS-CoV-2. *Science*. 2020; 368(6498):1422-4.
- [44] Sato T, Ueha R, Goto T, Yamauchi A, Kondo K, Yamasoba T. Expression of ACE2 and TMPRSS2 proteins in the upper and lower aerodigestive tracts of rats: implications on COVID 19 infections. *The Laryngoscope*. 2021; 131(3):E932-E9.
- [45] Amorim dos Santos J, Normando AGC, Carvalho da Silva RL, De Paula RM, Cembranel AC, Santos-Silva AR, Guerra ENS. Oral mucosal lesions in a COVID-19 patient: New signs or secondary manifestations? *International Journal of Infectious Diseases*. 2020; 97:326-8.
- [46] Cao Y, Li L, Feng Z, Wan S, Huang P, Sun X, et al. Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations. *Cell discovery*. 2020; 6(1):1-4.
- [47] Vaira LA, Salzano G, Petrocelli M, Deiana G, Salzano FA, De Riu G. Validation of a self-administered olfactory and gustatory test for the remotely evaluation of COVID-19 patients in home quarantine. *Head & neck*. 2020; 42(7):1570-6.
- [48] Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. *Frontiers of medicine*. 2020; 14:185-92.
- [49] Boymuradov SA, Rustamova DA, Bobamuratova DT, Kurbanov YX, Karimberdiyev BI, Yusupov SS, Umarov RZ. Complications of COVID-19 in the maxillo-facial region: Clinical case and review of the literature. *Advances in Oral and Maxillofacial Surgery*. 2021; 3:100091.
- [50] Arani R, Shareef S, Khanam HMK. Mucormycotic Osteomyelitis Involving the Maxilla: A Rare Case Report and Review of the Literature. *Case Rep Infect Dis*. 2019; 2019:8459296.
- [51] Thevissen K, Jacobs C, Holtappels M, Toda M, Verweij P, Wauters J. International survey on

influenza-associated pulmonary aspergillosis (IAPA) in intensive care units: responses suggest low awareness and potential underdiagnosis outside Europe. *Critical Care*. 2020; 24(1):84.

- [52] Ramires M, Mattia MB, Tateno RY, Palma LE, Campos L. A combination of phototherapy modalities for extensive lip lesions in a patient with SARS-CoV-2 infection. *Photodiagnosis Photodyn Ther*. 2021; 33:102196.
- [53] Van der Poel NA, Mourits MP, de Win MML, Coutinho JM, Dijkers FG. Prognosis of septic cavernous sinus thrombosis remarkably improved: a case series of 12 patients and literature review. *Eur Arch Otorhinolaryngol*. 2018; 275(9):2387-95.
- [54] Singh C, Tay J, Shoqirat N. Skin and Mucosal Damage in Patients Diagnosed With COVID-19: A Case Report. *J Wound Ostomy Continence Nurs*. 2020; 47(5):435-8.
- [55] Dima M, Enatescu I, Craina M, Petre I, Iacob ER, Iacob D. First neonates with severe acute respiratory syndrome coronavirus 2 infection in Romania: Three case reports. *Medicine (Baltimore)*. 2020; 99(33):e21284.
- [56] Riad A, Gad A, Hockova B, Klugar M. Oral candidiasis in non-severe COVID-19 patients: call for antibiotic stewardship. *Oral Surg*. 2022; 15(3):465-6.
- [57] Sakaida T, Tanimoto I, Matsubara A, Nakamura M, Morita A. Unique skin manifestations of COVID-19: Is drug eruption specific to COVID-19? *J Dermatol Sci*. 2020; 99(1):62-4.
- [58] Salehi M, Ahmadikia K, Badali H, Khodavaisy S. Opportunistic Fungal Infections in the Epidemic Area of COVID-19: A Clinical and Diagnostic Perspective from Iran. *Mycopathologia*. 2020; 185(4):607-11.
- [59] Salehi M, Ahmadikia K, Mahmoudi S, Kalantari S, Jamalimoghadamsiahkali S, Izadi A, et al. Oropharyngeal candidiasis in hospitalised COVID-19 patients from Iran: Species identification and antifungal susceptibility pattern. *Mycoses*. 2020; 63(8):771-8.
- [60] Dziedzic A, Wojtyczka R. The impact of coronavirus infectious disease 19 (COVID-19) on oral health. *Oral diseases*. 2021; 27:703-6.

Please cite this paper as:

Bolandparva F, Mohajeri Tehrani M, Heydari N. Oral and maxillofacial complications of COVID-19 infection: A review. *J Craniomaxillofac Res* 2023; 10(3): 86-98