



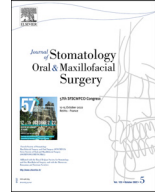
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Review

Oral mucosa lesions in confirmed and non-vaccinated cases for COVID-19: A systematic review



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ABSTRACT

This systematic review purposed to investigate reports of oral lesions in confirmed COVID-19 patients summarizing clinical characteristics, histological findings, treatment and correlation of oral lesions and COVID-19 severity. Electronic search was conducted on November 2021 using seven databases to identify case reports/series describing lesions in oral mucosa in COVID-19 confirmed cases. A total of 5,179 studies were found, being 39 eligible from 19 countries, totalling 116 cases. It was observed only COVID-19 non-vaccinated cases and no sex or age predilection. The oral lesions presentation was mostly single location (69.8%), commonly in the tongue, lips, and palate, being ulcer the main clinical presentation. According to severity index for COVID-19, the reports were more frequent in patients with mild and moderate symptoms, being 75.8% in acute phase. The oral lesion appearance in post-acute COVID-19 were described after 14 to two months after patient recovery. Histologically, keratinocytes with perinuclear vacuolization, thrombosis and mononuclear inflammatory infiltrate were also described with the presence of the virus in keratinocytes, endothelial cells, and minor salivary glands. In conclusion, health care professionals should consider COVID-19 association when patient present ulcerated oral lesions and mild to moderate symptoms for COVID-19 or had acute-COVID-19.

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1. Introduction

The Coronavirus Disease-19 (COVID-19) caused by SARS-CoV-2 virus, was firstly reported to WHO in 2019 New Year's Eve, as several cases of pneumonia of unknown cause in Wuhan City. The virus was identified on 7th January 2020 by Chinese researchers and since then spread rapidly worldwide infecting more than 432 million

individuals and causing 6.206.609 deaths until 20th April 2022 (<https://arcg.is/0fhmTX>).

Clinically, a variety of signs and symptoms are reported including oral lesions and oral disorders as dysgeusia (taste disorder) and dysphagia (difficulty swallowing). Since the first case series of oral lesion found in COVID-19 patients [1], some cases were in patients based on COVID-19 symptoms and not confirmed by SARS-CoV-2 testing. Moreover, studies have demonstrated high correlation of loss of taste and COVID-19 [2,3], however, it is not yet clear whether oral lesions, are indeed related to SARS-CoV-2 infection [1,4] and its severity, or is associated with other factors [5,6].

To better understand the relationship between COVID-19 infection and oral lesions, this study aimed to summarize the clinical characteristics, histological findings and the treatment of the oral lesions

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in SARS-CoV-2 positive patients and observe if there is any correlation with the severity of the COVID-19.

2. Materials and methods

This systematic review was performed according to the guidelines of the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocol) [7,8], and registered in the PROSPERO (International prospective register of systematic reviews) platform under number CRD42020222737.

2.1. Search strategies

An electronic search was carried on November 21st, 2021, using the Embase, LILACS, PubMed, SciELO, Scopus, LIVIVO and Web of Science databases. The following terms were used in the search strategies: "COVID-19", "SARS-COV-2", "2019 novel coronavirus disease", "2019-nCoV infection", "Oral Cavity", "Mouth", "Mucosal", "Lesion", "Infection", "Injuries", and "Injury". Boolean operators (AND and OR) were used to combine descriptors and improve the search strategy employing different combinations. The search strategies were adapted to each database respecting their rules of syntax (**Supplementary File 1**). A manual search was additionally performed on February 3rd, 2022

2.2. Studies selection and data extraction

Records were exported to the Mendeley software and to Rayyan QCRI software (Qatar Computing Research Institute, Doha, Qatar). Then duplicated records were excluded and selected independently by two reviewers (L.S. and M.A.L.S.). Later, full texts were retrieved and evaluated based on the inclusion and exclusion criteria. Disagreements between the two reviewers were resolved by a third reviewer (L.M.).

After selection, data of the eligible studies were extracted and included: (a) authors and year of publication; (b) study design; (c) country; (d) number of cases; (e) age and sex of participants (f) sites of oral manifestation; (g) clinical description of oral lesion, (h) systemic COVID-19 symptoms; (i) histopathological findings; (j) oral treatment; (k) medical history; (l) vaccination for COVID-19; (m) COVID-19 infection period when oral lesion appeared.

2.3. Eligibility criteria

Inclusion criteria was defined as case reports/series describing oral lesion in patients with positive results for COVID-19 by RT-PCR test and complete epidemiological data (participants' age, sex, COVID-19 severity, lesion location), reports presented as letters to the editor were also included. There were no limitations on publication year. Animal studies, *in vitro* studies, literature reviews, clinical trials, studies that were not case reports or case series, and case reports with different outcome or that did not present a confirmed COVID-19 test were excluded of present study. Only studies published in English language were considered.

2.4. Assessment of risk of bias of eligible studies

The Joanna Briggs Institute (JBI) Critical Appraisal Tools for use in Systematic Reviews for case reports and for case series were used to assess the risk of bias and the individual quality of the studies selected [9].

Each question of the checklists could be answered as "yes", if the study did not present bias regarding the domain evaluated by the question; "no", if the study presented bias regarding the domain assessed by the question; "unclear", if the study did not provide

sufficient information to evaluate the bias in the question; or "not applicable" if the question was not suitable for the study.

The risk of bias would be rated as high when the study reached up to 49% score "yes", moderate when it reached 50% to 69% score "yes", and low when it reached more than 70% score "yes".

2.5. Data analysis

All numerical data are presented as absolute values and percentage calculated using Microsoft Excel version 2202 (Microsoft). The Pearson's chi-squared test was used to observe the association between COVID-19 severity and age or sex or oral lesion. $P < 0.05$ was considered statistically significant.

3. RESULTS

3.1. Study selection results

A total of 5179 manuscripts were retrieved after the electronic databases search. There was 2596 duplicates and 2533 references excluded in the first screening. amongst full-text excluded studies, there were COVID-19 case reports or case series of oral lesions that did not report RT-PCR test for COVID-19 diagnosis or those describing confirmed COVID-19 cases that did not present oral lesions, remaining 27 articles for the assessment of the eligibility criteria. Another twelve records were identified through hand-searching, resulting in 39 eligible articles (**Supplementary File 2**). A flowchart depicting the selection process is provided in **Fig. 1**.

3.2. Risk of bias of the included studies

The majority of selected studies scored low risk of bias (33/39; 84.6%), while 12.8% (5/39) were moderate risk, and only one study shows high risk of bias (1/39; 2.6%).

The main shortcomings in the case reports studies were related to the insufficient description of the patients' clinical history and some case series studies presented scarce information about outcomes or follow up, and unclear reporting of the oral lesion site(s)/clinical aspects and demographic information. The risk of bias evaluation of all eligible articles is present in **Supplementary File 3 and 4**.

3.3. Characteristics of the selected studies

The selected articles comprise case reports (30/39; 76.9%) and case series (9/39; 23.1%) published between April/2020 and October/2021, all of them written in English language. Studies were conducted in nineteen different countries from four continents, eighteen of them located in Europe, eleven in America, eight in Asia and two in Africa.

3.4. Patients profile

A total of 116 patients, between 6 and 83 years-old, with COVID-19 confirmed by RT-PCR test. There was no report about vaccinated patients for COVID-19. The proportion male/female investigated was of 1:1.1, with slight predilection for female sex (**43/116; 53.4%**). Most lesion occurred during acute phase of COVID-19 (**88/116; 75.8%**), while 28 reports were in post-acute COVID-19 cases, occurring at 14 to two months after the recovery of patient.

The most common comorbidities were diabetes and hypertension, and only **20.6%** (24/116) of the cases had hospitalization history. All patients profile, medical history, COVID-19 symptomatology and severity, oral lesion characteristics and localization are presented in **Table 1**.

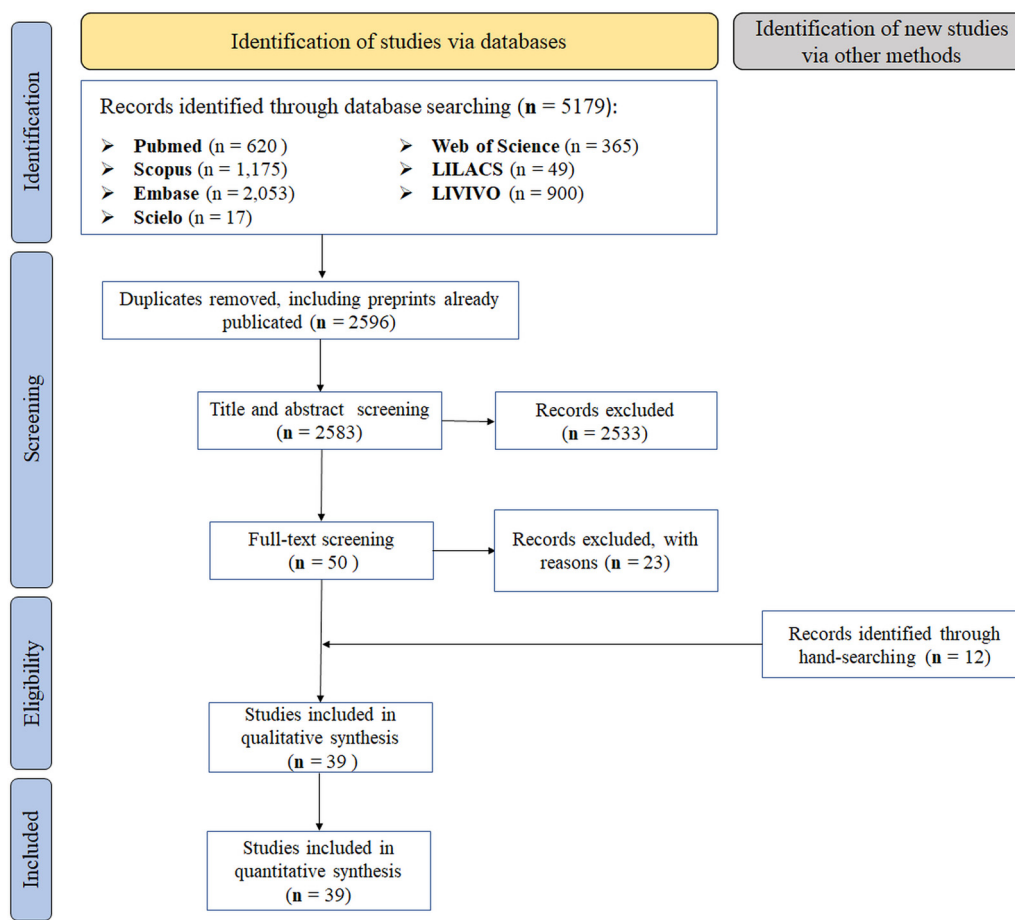


Fig. 1. Flow diagram of the study about oral lesions in non-vaccinated COVID-19 positive patients.

3.5. Frequent sites of oral lesions in COVID-19 patients

Regarding the localization of oral lesions in COVID-19 patients, the intrabuccal sites number were calculated based on the overall quantity present in the 116 cases, totalling 142 intrabuccal sites. Most cases presented single intraoral site involvement (69.8%), while multiple sites affected represented 31.2%.

The most common sites (Fig. 2A) were the tongue (57/142; 40.1%), followed by the lips and commissure (26/142; 18.3%), hard and soft palate (36/142; 25.4%), buccal mucosa (4/142; 2.8%), gingiva (4/142; 2.8%), and tonsillar pillar (2/142; 1.4%). Other sites affected, such as labial mucosa, floor of mouth and all over the mouth, consist of 9.2% (13/142) of the intraoral sites reported.

3.6. Type of oral lesions in COVID-19 patients

The selected studies presented a reduced number of COVID-19 patients with oral lesions that presented taste alterations (dysgeusia/ageusia, 12/116; 10.3%) or difficulty to swallowing (dysphasia, 5/116; 4.3%).

Regarding the clinical aspect of oral lesions (Fig. 2B), ulcerative lesions (57/116; 49.1%) was the most frequent clinical presentation with varied sizes, being local or multiple, sometimes with haemorrhagic areas, crust and necrosis. amongst ulcerative lesions (n = 57), most of them there were no specific cause (44/57; 77.2%), others were correlated with herpes simplex virus (HSV) co-infection (5/57; 8.7%) [10–12], or *Enterococcus faecalis* and/or *Pseudomonas aeruginosa* bacteria (2/57; 3.5%) [13] or associated with fungi as candidiasis (6/57; 10.5%) [14–17] and mucormycosis (23/116; 19.5%) [18–20].

The other lesions reported were diffuse erythema diagnosed as mucositis (14/116; 12%) [6,21]; angina bullosa haemorrhagic-like and associated vascular disorder (5/116; 4.3%) [22]; petechiae (2/116; 1.7%) [23,24] white plaque reported as candidiasis (5/116; 4.3%) [15,16] Tumoral lesion (2/116; 1.7%) [25,26] were also reported, being one case related to a Melkersson-Rosenthal syndrome [26], which is characterized by recurrent orofacial oedema, fissures in the tongue and peripheral facial paralysis and commissural fissures on lips.

Fig 3

3.7. COVID-19 severity and oral lesions

The COVID-19 severity was evaluated according to the National Health Institute (NIH) clinical spectrum of SARS-CoV-2 infection criteria, (<https://www.covid19treatmentguidelines.nih.gov/>) with the majority of the patients presenting mild (43/116; 37.2%) and moderate (38/116; 32.7%) symptoms, followed by severe cases (33/116; 28.4%), one critical case (1/116; 0.8%) [14], and one asymptomatic case (1/116; 0.8%) [17].

The univariate analysis of the association between COVID-19 severity and age or sex presented no statistically significant difference ($p = 0.0954$ and 0.5937 , respectively), while ulcer occurrence presented significance ($p = 0.0002$). (Table 2)

3.8. Histological and serological features

Only eight studies investigated histological features in oral lesions using haematoxylin and eosin staining (H&E) and immunohistochemistry (IHC) techniques.

Table 1
Case reports and case series of non-vaccinated COVID-19 patients' profile and clinical characteristics of oral lesions.

Author	Country	Sex (N)	Age (Year)	Location	Clinical Aspect (Oral lesion)	Oral Lesion Diagnostic	Oral Treatment	N of cases	COVID-19 Severity	COVID-19 Symptoms	Medical History	Infection Period	Hospitalization History
Abdelgawad et al., 2021*	Egypt	F	34	Lateral border of the tongue	White rough surface	Plaque	NI	1	Moderate	Loss of smell, mild fever, severe generalized bone aches and fatigue	NI	Post-acute COVID (2 months) [‡]	No
Aghazadeh et al., 2020	Iran	F	9	Lips and Tongue	Vesicular herpetiform oral eruption and acral erythematous papules and plaques	Vesicles and Erosions	NI	1	Severe	Fever, Pneumonia, skin eruption, abdominal pain, diarrhoea, dry cough, shortness of breath with tachypnoea and involving bilateral lungs	NI	During acute phase of COVID-19	No
Ahmed et al., 2021	Egypt	M(11) F	(10)	58 ± 12	Palate	Hard palate showing deep necrotic ulcer	Mucormycosis	NI	21	Severe	NI	NI	Post-acute COVID (14 days) [‡]
No Amorim dos Santos et al., 2020	Brazil	M	67	Tongue	Plaque centrally located, associated with several small, circle-shaped yellowish ulcers associated with candidiasis	Ulcer associated with Candidiasis	Nystatin	1	Critical	Fever, diarrhoea, and dyspnoea	Hypertension, coronary disease, kidney transplant	During acute phase of COVID-19	Yes
Ansari et al., 2020*	Iran	F	56	Hard palate	Painful small ulcers, with irregular margins, in red and non-haemorrhagic background	Ulcer	NI	2	Moderate	Fever and dyspnoea	Diabetes mellitus	During acute phase of COVID-19	No
		M	75	Tongue	Painful small ulcers, with irregular margins, in red and non-haemorrhagic background	Ulcer	Diphenhydramine, dexamethasone, tetracycline, and lidocaine		Moderate	Hypoxia	Hypertension	During acute phase of COVID-19	No
Brandão et al., 2020	Brazil	M	28	Lips and tongue	Aphthous-like ulcers	Ulcer	Non-alcoholic chlorhexidine	8	Mild	Cough, fever, headache, myalgia, and chills	Non-contributory	During acute phase of COVID-19	Yes
		M	29	Tongue	Ulcer with a whitish pseudomembrane surrounded by an erythematous halo	Ulcer	NI		Mild	Fever, cough, headache, dyspnoea on exertion, and general malaise	Non-contributory	During acute phase of COVID-19	Yes
		F	32	Tongue	Recurrent oral ulcers presenting an aphthous-like pattern	Ulcer	NI		Mild	Fever, cough, and headache	Non-contributory	During acute phase of COVID-19	Yes
		M	35	Tonsillar pillar	Ulceration with fibrinopurulent membrane and surrounded by an erythematous halo	Ulcer	NI		Moderate	Fever, cough, sore throat, and general malaise	Non-contributory	During acute phase of COVID-19	Yes
		F	71	Lips and tongue	Small haemorrhagic ulcerations	Ulcer associated with HSV	NI		Severe	Cough, dysgeusia, fever, and mild dyspnoea	Hypertension, diabetes, obesity, history of bariatric surgery and fibromyalgia, renal failure	During acute phase of COVID-19	Yes
		M	72	Lips	Small haemorrhagic ulcerations and necrotic ulcerations	Ulcer associated with HSV	Photo-biomodulation therapy		Mild	Severe acute respiratory syndrome, cough, dysgeusia, fever, and mild dyspnoea	Diabetes and hypertension	During acute phase of COVID-19	Yes
		M	81	Lips and Tongue	Multiple shallow aphthous-like ulcers of varying sizes and irregular margins	Ulcer associated with HSV	Photo-biomodulation therapy		Severe	Cough, chills and fever	Controlled hypertension and chronic obstructive pulmonary disease	During acute phase of COVID-19	Yes
		F	83	Tongue and hard palate	Ulcer	Ulcer	Photo-biomodulation therapy		Mild	Abdominal distension, mild dyspnoea and lung	Obesity, Parkinson disease, hypertension,	During acute phase of COVID-19	Yes

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Table 1 (Continued)

Author	Country	Sex (N)	Age (Year)	Location	Clinical Aspect (Oral lesion)	Oral Lesion Diagnostic	Oral Treatment	N of cases	COVID-19 Severity	COVID-19 Symptoms	Medical History	Infection Period	Hospitalization History
Binois et al., 2020	France	M	57	Lips and tongue	Haemorrhagic ulcers	Ulcer	NI	1	Severe	CT showed discrete hyperdense areas in both lungs	pancreatitis, and chronic obstructive pulmonary disease	During acute phase of COVID-19	Yes
Cabeci Kahraman et al., 2020	Turkey	F	67	Lips	Haemorrhagic crust	Crust	Triticumvulgare extract	1	Moderate	Cough, headache, myalgia, fever	NI	During acute phase of COVID-19	No
Chaux-Bodard et al., 2020	France	F	45	Tongue	Painful ulcer	Ulcer	NI	1	Mild	Fatigue	NI	During acute phase of COVID-19	No
Cicarese et al., 2020	Italy	F	19	Lip and gingiva	Erosions, ulcerations, blood crusts and petechiae (thrombocytopenia)	Vascular disorder	NI	1	Moderate	NI	NI	During acute phase of COVID-19	No
Corchuelo & Ulloa, 2020	Colombia	F	40	Lower lips, gingiva and tongue	Reddish plaques on the lower lip and the appearance of dark brown pigmentation in the gum	Plaque associated with candidiasis and petechiae	Nystatin, chlorhexidine, and sodium hypochlorite solution	1	Moderate	Asymptomatic	Asymptomatic	NI	During acute phase of COVID-19
No Cruz Tapia et al., 2020*	Peru	M	42	Hard Palate	Multiple and irregular reddish macules	Nonspecific localized vasculitis and thrombosis	Chlorhexidine and mometasone furate	4	Moderate	Myalgia, dysgeusia, headache, fever, and burning mouth symptoms	NI	During acute phase of COVID-19	No
Dalipi et al., 2021	Kosovo	F	41	Hard palate and tongue	Erythematous bulla, non-bleeding vascular-like purple macule, purple bulla, multiple reddish macules	Angina bullosa haemorrhagic-like	NI	1	Moderate	Fever, myalgia, dysphagia, and hyposmia	NI	During acute phase of COVID-19	No
Diaz Rodríguez et al., 2020	Spain	F	43	Tongue	Diffuse vascular-like purple macule	Vascular disorder	Chlorhexidine	1	Moderate	Fever, myalgia, dysphagia, and articular pain	NI	During acute phase of COVID-19	No
Eghbali Zarch & Hosseini-deh, 2021	Iran	F	56	Lower lip	Aphthous-like lesions, burning sensation, and depapillation	Ulcer	Triamcinolone acetonide	3	Severe	Fever, malaise, dysgeusia and anosmia, diarrhoea, and pneumonia	NI	During acute phase of COVID-19	No
Fathri et al., 2021	Iran	F	22	Oral mucosa and Lips	Commissural fissures	Erosion	Neomycin, nystatin, and triamcinolone	1	Severe	Fever, headache, and nasal congestion	NI	During acute phase of COVID-19	No
Glavina et al., 2020	Croatia	F	40	Hard Palate	White patches, distributed mainly in the left lateral side, and a red plaque located in the hard and soft palate	Plaque associated with candidiasis	Nystatin	1	Moderate	Fever, cough, headache, muscle pain, and loss of taste and smell	NI	During acute phase of COVID-19	No
Gabusi et al., 2021*	Italy	M	78	Lower Lip	Vesicle	Ulcer associated with HSV	NI	1	Moderate	High fever, fatigue, and dysphagia	Hypertension and chronic sinusitis. Previous history of herpetic infections	During acute phase of COVID-19	Yes
					Extensive mucosal ulcers in the oral cavity and haemorrhagic crusts on the lips	Ulcer	Chlorhexidine	1	Severe	Fever, abdominal pain, nausea and occasional vomiting	NI	During acute phase of COVID-19	Yes
					Painful ulcerated plaque of the mucosal side of the lower lip.	Ulcer	Acyclovir	1	Mild	Weakness, fever, aguesia	NI	During acute phase of COVID-19	No
						Ulcer and Plaque	Hydroxychloroquine, steroids,	1	Severe	Severe pneumonia and acute respiratory distress	Previous diagnosis of follicular lymphoma	Post-acute COVID (6 months)§	Yes

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Table 1 (Continued)

Author	Country	Sex (N)	Age (Year)	Location	Clinical Aspect (Oral lesion)	Oral Lesion Diagnostic	Oral Treatment	N of cases	COVID-19 Severity	COVID-19 Symptoms	Medical History	Infection Period	Hospitalization History
Hocková et al., 2021a	Slovakia	M	61	Tongue and Lips	Haemorrhagic ulcers along focal necrosis	Ulcer caused by bacterium (<i>Enterococcus faecalis</i> and <i>Pseudomonas aeruginosa</i>)	NI ciprofloxacin, and toclizumab	3	Severe	Pneumonia	Obesity, arterial hypertension, previous history of myocardial infarction and septic shock.	During acute phase of COVID-19	Yes
Hocková et al., 2021b	Slovakia	F	26	Lower Lip	Minor aphthous stomatitis of the lower lip, painful on palpation	Ulcer	NI	1	Moderate	Sore throat, headache, myalgia, and fatigue	NI	During acute phase of COVID-19	No
Hock et al., 2021	England	M	21	Palate	Petechia	Petechia	NI	1	Moderate	Sore throat, epistaxis	N	During acute phase of COVID-19	Yes
Kiatakawa et al., 2020 ^{a2}	Brazil	F	20	Lower Lip	Ulcer	Ulcer	Nebacetin ointment	1	Mild	Sore throat and headache	NI	During acute phase of COVID-19	No
Selarka et al., 2021	India	M	42	Hard Palate	Ulcerative eschar at the hard palate	Mucormycosis	NI	1	Moderate	Fever, running nose, dry cough with generalized malaise	Diabetes	During acute phase of COVID-19	Yes
Labé et al., 2020	France	M	6	Upper, Lower Lips, gingiva	Severe erosive cheilitis with diffuse gingival erosions and thick haemorrhagic crusts	Ulcer and Erosion	NI	1	Moderate	Rash of the extremities, and anosmia	NI	During acute phase of COVID-19	Yes
Liang et al., 2020	China	M	41	Tongue	Petechia	Petechiae	NI	1	Moderate	Fever, cough, chills, fatigue, dyspnoea	NI	During acute phase of COVID-19	Yes
Malih et al., 2020	Iran	M	38	Left Tonsil	Erythema and aphthous lesion on the left tonsil	Ulcer	NI	1	Moderate	Fever, fatigued and myalgia	NI	During acute phase of COVID-19	No
Medeiros & Guimarães, 2021	Brazil	F	78	Tongue and Labial mucosa	Erosive lesions with circumscribed halos, of different sizes along the entire length of the dorsum, bilateral margins of the tongue and labial mucosa	Erosion	Nystatin and artificial saliva spray	1	Severe	Pain in the mouth, dysgeusia and odynophagia	NI	Post-acute COVID (15 days) [†]	Yes
McGoldrick et al., 2021	England	M	53	Tongue and floor of mouth	Tongue and floor of mouth swelling	Tumour	NI	1	Moderate	NI	NI	During acute phase of COVID-19	Yes
Kämmerer et al., 2021*	Germany	M	46	Buccal mucosa	Ulcer	Ulcer	Aciclovir	1	Moderate	Fatigue, dry cough, and fever	NI	During acute phase of COVID-19	No
Nejati et al., 2021	Afghanistan	M	62		M	62	Tongue	White	geographic ulcer with irregular borders	Ulcer	Photo-biomodulation therapy, Chlorhexidine and H2O2	1	Mild
Fever, cough, dysgeusia, olfactory dysfunction, and chest tightness	Diabetes mellitus-type-2 and moderate			hypertension.	During acute phase of COVID-19	Yes							
Orcina & Santos, 2021	Brazil	M	29	Lip	Ulcer	Ulcer	Phalox® mouthwash	4	Mild	Sore throat, body aches, fever, cough, anosmia, dysgeusia	NI	During acute phase of COVID-19	No

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Table 1 (Continued)

Author	Country	Sex (N)	Age (Year)	Location	Clinical Aspect (Oral lesion)	Oral Lesion Diagnostic	Oral Treatment	N of cases	COVID-19 Severity	COVID-19 Symptoms	Medical History	Infection Period	Hospitalization History
		F	30	Lip	Ulcer	Ulcer	Phtalox® mouthwash		Mild	Sore throat, body aches, diarrhoea, fatigue, and cough	NI	During acute phase of COVID-19	No
		M	32	Lip	Ulcer	Ulcer	Phtalox® mouthwash		Mild	Body aches, cough, and chills	NI	During acute phase of COVID-19	No
		M	52	Tongue	Ulcer	Ulcer	Phtalox® mouthwash		Moderate	Acute sore throat and constant cough	Smoker	During acute phase of COVID-19	No
Pauli <i>et al.</i> , 2021*	Brazil	F	50	Hard palate	Small ulcer lesion	Mucormycosis	NI	1	Mild	Persistent headache	Type 2 diabetes	During acute phase of COVID-19	No
Riad <i>et al.</i> , 2020a	Czech Republic	No			9 M / 17 F	36.81 ± 15.65	Tongue	Ulcer	Ulcer	Chlorhexidine	26	20 Mild 6 Moderate	Fever, cough, ageusia, sore throat
Non-contributory													
Riad <i>et al.</i> , 2020b	Czech Republic				5 M / 8 F	51.08 ± 8.79	All over the mouth (7), Palate and buccal mucosa (1), Buccal mucosa (3), Hard and soft palate (1), Gingiva (1)	Sporadic	erythema with minor irritations sites	described. All cases presented depapillation of the tongue with a tendency to be more localized at the borders	Mucositis	Chlorhexidine and prednisolone	13
9 Mild 4 Moderate	Fever, ageusia,			anosmia	NI	During acute phase of COVID-19	No						
Riad <i>et al.</i> , 2021	Czech Republic				F	70	Tongue dorsum, mouth floor, and soft palate	White	membranous patches spread over the tongue dorsum, mouth floor, and soft palate	Patches associated with Candidiasis	Nystatin and Chlorhexidine	3	Moderate
Burning sensation and dysphagia	Geriatric depression, peripheral neuropathy, urinary incon-			tinence, chronic constipation, and vascular disease	During acute phase of COVID-19	Yes							
		F	25	Tongue dorsum	Erythematous candidiasis over the tongue dorsum	Patches associated with erythematous candidiasis	NI		Moderate	Fatigue, headache, anosmia, and ageusia	NI	During acute phase of COVID-19	No
		F	56	Labial mucosa, and soft palate and tongue dorsum	White membranous patches extended over labial mucosa, and soft palate and tongue dorsum	Patches associated with Candidiasis	Miconazole (Gel)		Moderate	Dysphagia and abdominal pain	Diabetes mellitus type 2 and rheumatoid arthritis	During acute phase of COVID-19	No
Soares <i>et al.</i> , 2020*	Brazil	M	42	Hard palate, tongue, and lips	Oral reddish lesions and ulceration	Ulcer	NI	1	Moderate	Fever, cough, and dyspnoea	Diabetes and hypertension	During acute phase of COVID-19	No
Soares <i>et al.</i> , 2021*	Brazil	M	23	Lips	Vesiculobullous lesions with an erythematous halo	Vesicle and Ulcer	Systemic dexamethasone	1	Moderate	Fever and dry cough	NI	During acute phase of COVID-19	No
Taslidere <i>et al.</i> , 2020	Turkey	F	51	Lower lip, tongue	Firm oedema in the right lower lip	Tumour	NI	1	Severe	Fever	Melkersson-Rosenthal Syndrome	During acute phase of COVID-19	Yes
Tomo <i>et al.</i> , 2020	Brazil	F	37	Tongue and hard palate	Oral mucositis with diffuse erythema with some petechia and discrete depapillation	Mucositis	Chlorhexidine	1	Mild	Fever	NI	During acute phase of COVID-19	No

(*), Studies presenting histological findings. M, male. F, female. NI, not informed. N, number of cases. (‡) period post-COVID-19 recovery.

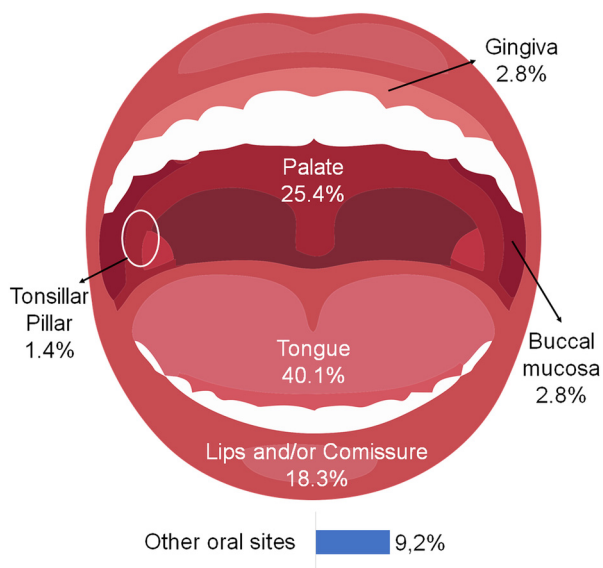


Fig. 2. Oral sites and frequency of lesions in confirmed cases of COVID-19.

In general, the haematoxylin and eosin staining showed focal exocytosis and paranuclear keratinocytes vacuolization in epithelium. The lamina propria presents mononuclear inflammatory infiltrate, vascular thrombosis, and can present haemorrhagic and necrotic focal areas.

According to Soares *et al.* (2020)[27] observations, the inflammatory infiltrate presents on these lesions are composed by T CD3 and T CD8 cells. The CD3 positive cells are present in the basal layer of epithelium and surrounding endothelial cells in the connective, while CD8 positive cells were present in lamina propria.

The spike-protein immunoreactivity was used to identify SARS-CoV-2 virus in ulcerated tissues of the hard palate, tongue, buccal

mucosa, and lips. Positive reaction for spike-protein was found in endothelial cells, keratinocytes, acinar and ductal cells of the minor salivary glands [28].

Serological technique was applied to investigate antibodies against Herpes Simplex Virus (HSV) type-1 and type-2 in small ulcers for differentiating the diagnostic. The authors had negative results for both HSV types and suggested that the ulcerative lesions can be potentially induced by the new coronavirus. [27–29]

Most histological analyses were described during acute phase of the infection, and two studies reported occurrence of persistent alterations in the post-acute COVID-19. Abdelgawad *et al.* (2021)[30] described the presence of verrucous leucoplakia in lateral border of the tongue with microscopical findings of mild-moderate dysplasia and absence of malignancy. Gabusi *et al.* (2021)[29] mentioned the occurrence of oral ulcerative lesions and erosive plaques in the lower lip and gingiva of a patient with a lymphoma history. Immunohistochemical results for HSV 1, HSV 2, and CMV biomarkers were negative. The H&E revealed the presence of ulceration with granulation tissue and fibrin-leucocytic jointly to dense inflammatory infiltrate.

3.9. Oral lesion treatments

The oral lesions were treated with different pharmacological protocols: with 0.12% chlorhexidine mouthwash, steroidal anti-inflammatories, antibiotics, Photobiomodulation therapy, antifungal, retroviral or herbal treatment. Specific details of treatment applied by each oral lesion are shown in Table 1.

4. Discussion

The COVID-19 is a complex disease, capable of causing a wide spectrum of severity classified as asymptomatic; mild, presenting fever, dry cough, anosmia, dysgeusia, and fatigue; moderate, when the patient starts to present hypoxia; severe illness when present oxygen saturation under 94%, dyspnoea; critical illness, respiratory

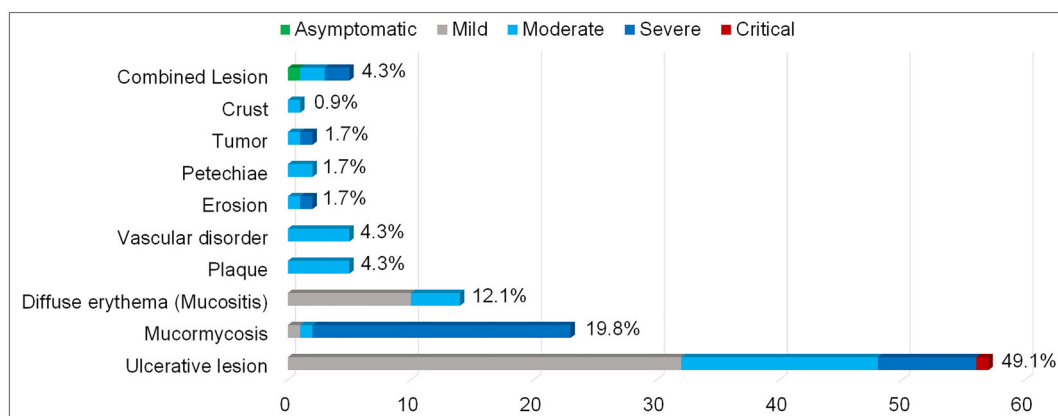


Fig. 3. Clinical aspect of oral lesions and frequency according to COVID-19 severity.

Table 2

Analysis of the association between clinical variables of patients with oral lesions and COVID-19, according to disease severity.

Clinical Variables	Number of cases	Asymptomatic	Mild	Moderate	Severe	Critical	P-value*
Age (Years) (n = 56)							0.0954
< 50	30	1 (1.8%)	10 (17.9%)	16 (28.6%)	3 (5.3%)	0 (0.0%)	
≥ 50	26	0 (0.0%)	4 (7.1%)	12 (21.4%)	9 (16.1%)	1 (1.8%)	
Sex (n = 56)							0.5937
Male	29	0 (0.0%)	6 (10.7%)	16 (28.6%)	6 (10.7%)	1 (1.8%)	
Female	27	1 (1.8%)	8 (14.3%)	12 (21.4%)	6 (10.7%)	0 (0.0%)	
Oral Lesion (n = 116)							0.0002
Ulcer	57	0 (0.0%)	32 (27.6%)	16 (13.8%)	8 (6.9%)	1 (0.8%)	
Others	59	1 (0.8%)	11 (9.5%)	22 (19.0%)	25 (21.6%)	0 (0.0%)	

*P-value for Chi-square. Significant when P-value < 0.05.

failure, septic shock, and/or multiple organ dysfunction or failure, that can culminate in death [31]. Most of these severe/critical symptoms are more frequent in elderly individuals, males, and patients with obesity, cardiac and metabolic disorder, and chronic diseases and seems to be due to an immunopathological process that causes exceeded production of cytokines [32].

In the present study, the ulcer was the lesion more commonly reported and tongue the main anatomical area described by authors. Previous review[33] found a slight predisposition to the appearance of ulcers in patients with COVID-19, suggesting as a potential pathognomonic sign for early diagnosis of the disease.

According to the selected literature in our study, it was found a slight predominance of oral lesions in women, but no statistical significance. Some studies have demonstrated that is not possible to suggest any predictable profile for oral mucosa lesions occurrence in COVID-19 patients since both genders are equally affected [4,6]. On the other hand, higher dysfunction of the gustatory system in female patients with COVID-19 were suggested to be related to an exacerbated hormonal modulation and immune innate response to viral infection in those patients [34].

Despite, the limitation of the study to find a greater number of reports describing confirmed cases of COVID-19 with complete information about patients' clinical aspect, and oral lesions details, it was possible to observe that most of the cases reported showed mild and moderate severity for COVID-19, and there was statistical significance in ulcer occurrence in those patients.

In general, it was observed a diversified clinical aspect of oral mucosal lesions in COVID-19 patients, such as vesicles, macules, plaques, blisters, erythema, petechia and ulcers. Interestingly, vascular alterations in oral cavity were also reported in COVID-19 patients [22]. Recent publications have supported the association of oral mucosa lesions related to COVID-19 with complications for thrombocytopenia, anticoagulant therapy, disseminated intravascular coagulation, and systemic inflammation [21,22,28]. Histopathological analysis have demonstrated that early oral lesions also present thrombosis of small and middle size vessels was always noticed with necrosis of superficial tissues [35]. These features are not exclusive to oral cavity, several studies demonstrates the predispose of COVID-19 patients to develop haematologic diseases that may result in thrombosis, especially, as consequence of vasculitis [36,37].

Considering the period of oral lesions appearance, most cases reported their occurrence in COVID-19 patients during acute phase. On the other hand, fewer cases occurred during post-acute COVID-19 infection [20,29,30]. There still little evidence about the real cause of these oral lesions related to post-acute COVID-19. Ulceration[20,29], erosion and a verrucous leucoplakia[30] were described, and authors suggested as a probable hypothesis the SARS-CoV-2 capacity in leading to reactivation of viruses like the herpes virus' family [29,30]. Despite evidence about the presence of SARS-CoV-2 in oral tissue [28], more studies are still needed to understand the pathogenesis of oral lesions related to COVID-19 and secondary causes cannot be excluded.

The oral health can also interfere in patients' recovery and COVID-19 severity. It was observed in a cross-sectional study observing protein C-reactive (PCR) levels in COVID-19 patients, their oral health and disease evolution [38]. They observed that the fast recovery period was present in 82% of the patients with good oral health and high PCR levels were related to poor oral health and severe cases, respectively [38]. Therefore, critical attention should be given to providing efficient oral hygiene to ill COVID-19 patients, especially in severe cases.

Interestingly, to date, although more than 10 billion doses of vaccine have been already administered around the world, (<https://arcg.is/OfHmTX>) we could not find any reports of oral lesions in patients infected with SARS-CoV-2 after receiving the vaccination. Curiously,

evidence about oral lesions as side effects after vaccination already exists[39] and are similar to the oral findings' characteristics in infected patients with SARS-CoV-2. The most prevalent oral side effect are vesicles, bleeding gingiva, halitosis, oral paraesthesia, swollen mucosa, and ulcers, emerging within the first week after vaccination in more than 75% of the cases[39], similarly to the frequency of oral findings in acute-COVID-19 presented in our study.

In conclusion, COVID-19 patients seem to present more frequently oral ulcerations in mild and moderate illnesses, independent of age or sex. A detail oral examination is recommended in suspected and diagnosed cases of COVID-19 patients. The multidisciplinary approach in which dental health care professionals should be aware of infectious and vascular diseases associated with COVID-19 is for the better of patients' premature diagnostic and prognostic.

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Declaration of Competing Interest

All authors declare there is no financial interest to report, confirming that there is no potential conflict of interest.

Confirmation of patient permission

Patient permission/consent not applicable.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jormas.2022.05.005](https://doi.org/10.1016/j.jormas.2022.05.005).

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