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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 post-acute COVID-19. 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.

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 that 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.
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 andMeta-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 2956 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 showed 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.
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%)[14,16] 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 peripheric facial paralysis and commissural fissures on lips.

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 (33/116; 28.4%) 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.
| Author et al., 2021 | Author Country | Sex | 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 | Fever, Pneumonia, skin eruption, abdominal pain, diarrhea, dry cough, shorness of breath with tachypnoea and involving bilateral lungs | NI | Post-acute COVID (2 months); | No |
| Aghazadeh et al., 2020 | Iran | F 9 | Lips and Tongue | Vesicular herpetiform oral eruption and axial erythematous papules and plaques | Vesicles and Erosions | NI | 1 | Severe | | | 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 | Mucoecymosis | NI | 21 | Moderate | Fever and dyspnoea | Diabetes mellitus | During acute phase of COVID-19 | No |
| Amorim dos Santos et al., 2020 | Brazil | M 67 | Tongue | Ulcer associated with Candidiasis | Nystatin | 1 | Critical | Fever, diathesis, and dyspnoea | Hypertension, coronary disease, kidney transplant | During acute phase of COVID-19 | Yes |
| Ansari et al., 2020* | Iran | F 56 | Hard palate | Ulcer | Diflunisyl, desoxycorticosterone, tetracycline, and lidocaine | Moderate | Hypoxia | | | | | | No |
| Brandao et al., 2020 | Brazil | M 28 | Lips and tongue | 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 | | 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 friable parotid 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 ulcers | Ulcer associated with HSV | NI | Severe | Cough, dysnea, fever, and mild dyspnoea | Hypertension, diabetes, obesity, respiratory dysfunction and chronic obstructive pulmonary disease | During acute phase of COVID-19 | Yes |
| | | M 72 | Lips | Small haemorrhagic ulcers and necrotic ulcerations | Ulcer associated with HSV | Photo-biomodulation therapy | Mild | Severe acute respiratory syndrome, cough, dysnea, fever, and mild dyspnoea | Diabets 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 | | | | | | | | | | | | | |
| Author                        | Country       | Sex | Age  | Location                  | Clinical Aspect (Oral lesion) | Oral Lesion Diagnostic | Oral Treatment | N of cases | 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            | Cough, headache, myalgia, fever, fatigue  | NI During acute phase of COVID-19 | Yes                     |
| Gobeci, Kaltman et al., 2020 | Turkey        | F   | 67   | Lips                       | Haemorrhagic crust            | Crust                   | Tretinoin vulgar extract | 1          | Moderate          | NI                                         | NI During acute phase of COVID-19 | No                      |
| Chaz - Bodart et al., 2020   | France        | F   | 45   | Tongue                     | Painful ulcer                | Ulcer                   | NI                | 1          | Mild              | NI                                         | NI During acute phase of COVID-19 | No                      |
| Giaccone et al., 2020        | Italy         | F   | 19   | Lip and gingiva            | Erosions, ulcerations, blood crusts and petechiae (Thrombocytopenia) | NI | T | 1 | Moderate | Fever, headache, fatigue, hypoxemia and sore throat | NI During acute phase of COVID-19 | No                      |
| Gocchuelo & Ulioa, 2020      | Colombia      | F   | 40   | Lower lips, gingiva and tongue | Reddish plaques on the lower lip and the appearance of dark brown pigmentation in the gums | Plaque associated with candidiasis and petechiae | Nystatin, chlorhexidine, and sodium hypochlorite solution | 1 | Asymptomatic | Asymptomatic | NI During acute phase of COVID-19 | No |
| No                           | Peru          | M   | 42   | Hard Palate                | Multiple and irregular reddish macules | Non-specific localized vasculitis and thrombosis | Chlorhexidine and mometasone furoate | 4 | Moderate | Myalgia, dysgeusia, headache, fever, and breathing | NI During acute phase of COVID-19 | No                      |
| No                           | Peru          | F   | 41   | Hard palate and tongue     | Erythematous bullae, non-bleeding vacular-like bullae, and purple bullae | Angina bullae haemorrhagic-like | NI | T | 1 | Moderate | Fever, myalgia, dysphagia, and hypoxemia | NI During acute phase of COVID-19 | No                      |
| F                            | Peru          | F   | 51   | Palate                     | Diffuse vacular-like purppla bullae | Angina bullae haemorrhagic-like | NI | T | 1 | Moderate | Fever, headache, and nasal congestion | NI During acute phase of COVID-19 | No                      |
| Dalapi et al., 2021          | Kosovo        | M   | 17   | Upper and Lower Lips and tongue | Ulcer                        | Ulcer                                 | Chlorhexidine | 1 | Moderate | Fever, cough, headache, muscle pain, and loss of taste and smell | NI During acute phase of COVID-19 | No                      |
| Diaz Rodriguez et al., 2020  | Spain         | F   | 43   | Tongue                     | Aphthous-like lesions, burning sensation, and desquamated ulcers | Ulcer                    | Triamcinolone acetonide | 3 | Severe | Fever, malaise, dysgeusia and anosmia, diarrhea, and pneumonia | NI During acute phase of COVID-19 | No                      |
| M                            | Spain         | M   | 53   | Lips                       | Granulomatous bullae         | Erosion                  | Neomycin, nystatin, and trimethadione | Moderate | Moderate | Anosmia and dysgeusia | NI During acute phase of COVID-19 | No                      |
| M                            | Spain         | M   | 78   | Tongue, palate, and lip (commissure) | 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 | Moderate | Anosmia and dysgeusia | NI During acute phase of COVID-19 | No                      |
| Iqbal Zarch & Hossennia-Deh, 2021 | Iran         | F   | 56   | Lower lip                  | Vesicle                     | Ulcer associated with HSV | NI | T | 1 | Moderate | High fever, fatigue, and dysphagia | Hypertension and chronic sinusitis, Previous history of herpetic infections | NI During acute phase of COVID-19 | No                      |
| Fallsi et al., 2021          | Iran          | F   | 22   | Oral mucosa and Lips       | 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                     |
| Giovina et al., 2020         | Croatia       | F   | 40   | Hard Palate                | Ulcer                       | Ulcer associated with HSV | Acyclovir | 1 | Mild | Weakness, fever, and tachypnea | NI During acute phase of COVID-19 | No                      |
| Gabusi et al., 2021*         | Italy         | M   | 78   | Lower Lip                  | Painful ulcerated plaque over the mucosal side of the lower lip. | Ulcer and Plaque         | Hydroxychloroquine, steroids | 1 | Moderate | Severe pneumonia and acute respiratory distress | Previous diagnosis of follicular lymphoma | Yes | Yes                     |

(continued on next page)
| Author Country, Year | Sex | 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 | M   | 61         | Tongue and Lips | Haemorrhagic ulcers along focal necrosis | Ulcer caused by bacteria (Enterococcus faecalis and Pseudomonas aeruginosa) | Ciprofloxacin, and ticlopidine | 3          | Severe            | Pneumonia         | Obesity, arterial hypertension, previous history of myocardial infarction and septic shock. | During acute phase of COVID-19 | Yes            |
|                      |     | 64         | Lips      | Focal painful lesions resembling haemorrhagic ulcerations | Ulcer | NI | Severe | Fever, dyspnoea, and dry cough | NI | During acute phase of COVID-19 | Yes            |
|                      |     | 68         | Tongue    | Ulcer caused by bacteria (Pseudomonas aeruginosa) | Ulcer | NI | Severe | Headache, fever, dry cough, and dysgeusia | NI | During acute phase of COVID-19 | Yes            |
|                      | 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             |
|                      | M   | 21         | Palate    | Petchia | Ulcer | NI | 1     | Moderate | Sore throat, epistaxis | N | During acute phase of COVID-19 | Yes            |
|                      |     | 20         | Lower Lip | Ulcer | Nebacetin ointment | 1 | Mild | Sore throat and headache, fever, running nose, dry cough with generalized muscle rash of the extremities and anosmia | Diabetes | During acute phase of COVID-19 | Yes            |
| Labi et al., 2020   | M   | 6          | Upper, Lower Lips, gingiva | Severe erosive cheilitis with diffuse gingival erosions and thick haemorrhagic crusts | Ulcer and Erosion | NI | 1     | Moderate | Sore throat, headache, myalgia, and fatigue | NI | During acute phase of COVID-19 | Yes            |
|                      |     | 41         | Tongue    | Petchia | Ulcer | NI | 1     | Moderate | Fever, cough, chills, fatigue, dysgeusia and odynophagia | N | During acute phase of COVID-19 | Yes            |
|                      | M   | 38         | Tonsil    | Erythema and aphthous lesion on the left tonsil | Ulcer | NI | 1     | Moderate | Fever, fatigue and myalgia | N | During acute phase of COVID-19 | Yes            |
|                      |     | 78         | Tongue and Labial mucosa | Erosion | Nystatin and artificial saliva spray | 1 | Severe | Fever, fatigue, dysgeusia and odynophagia | Diabetes | Post-acute COVID (15 days) | Yes            |
|                      | M   | 53         | Tongue and floor of mouth | Tongue and floor of mouth swelling | Ulcer | NI | 1     | Moderate | Fatigue, dry cough and fever | NI | During acute phase of COVID-19 | Yes            |
|                      |     | 46         | Buccal mucosa | Ulcer | Aciclovir | 1 | Moderate | N | Photo-biomodulation therapy, Chlorhexidine and HO2 | No | During acute phase of COVID-19 | No             |
|                      |     | 62         | Tongue    | White | Ulcer | NI | 4     | Mild | Sore throat, body aches, fever, cough, anosmia, dysgeusia | NI | During acute phase of COVID-19 | No             |
|                      | M   | 29         | Lip       | Ulcer | Phtalox® mouthwash | 4 | Mild | Sore throat, body aches, fever, cough, anosmia, dysgeusia | Diabetes mellitus type-2 and moderate hypertension. | During acute phase of COVID-19 | No             |

(continued on next page)
| 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, fatigue, and cough | Nil         | During acute phase of COVID-19 | No               |                |                  |                   |
| M 32                           | Lip                | Ulcer   | Ulcer      | Phtalox* mouthwash            | Mild                  | Body aches, cough, and chills             | Nil         | 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 et al., 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 et al., 2020a**         | Czech Republic     | 9 M / 1 F| All over the mouth | Ulcer | Chlorhexidine      | 26                  | Fever, cough, anosmia, sore throat |            |                  |                  |                |                  |                   |
| **Riad et al., 2020b**         | Czech Republic     | F 51    | All over the mouth | Ulcer | Chlorhexidine and prednisolone | 3                  | Fever, cough, aguesia, sore throat |            |                  |                  |                |                  |                   |
| **Riad et al., 2021**          | Czech Republic     | F 56    | All over the mouth | Ulcer | Chlorhexidine      | 1                  | Fever, cough, and dry cough | Diabetes mellitus | During acute phase of COVID-19 | No               |                |                  |                   |
| **Soares et al., 2020**        | Brazil             | M 42    | Hard palate | Oral reddish lesions and ulcer | Ulcer | Fever and dry cough | Diabetes and hypertension | During acute phase of COVID-19 | No               |                |                  |                   |
| **Soares et al., 2021**        | Brazil             | M 23    | Lips       | Vesiculobullous lesions with an erythematous halo | Vescicle and Ulcer | Fever and dry cough | Diabetes and hypertension | During acute phase of COVID-19 | No               |                |                  |                   |
| **Taslidere et al., 2020**     | Turkey             | F 51    | Lower lip  | Firm oedema in the right lower lip | Ulcer | NI 1 Severe | Fever | Meltzersson- Rosenbenth Syndrome | During acute phase of COVID-19 | Yes |                |                  |
| **Tomo et al., 2020**          | Brazil             | F 37    | Tongue and hard palate | Oral mucositis with diffuse erythema with some petechia and discrete depapillation | Mucositis | Chlorhexidine | 1 Mild | Fever | Diabetes | During acute phase of COVID-19 | No               |                |                  |                   |

(*), Studies presenting histological findings. M, male. F, female. NI, not informed. N, number of cases. (z) period post-COVID-19 recovery.
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) 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) described the presence of verrucous leukoplakia in lateral border of the tongue with microscopical findings of mild-moderate dysplasia and absence of malignancy. Gabusi et al. (2021) 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, retrovirial 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 mucosa, and lips. Positive reaction for spike-protein was found in endothelial cells, keratinocytes, acinar and ductal cells of the minor salivary glands [28].

Table 2

| Clinical Variables       | Number of cases | Asymptomatic | Mild | Moderate | Severe | Critical | P-value* |
|--------------------------|-----------------|--------------|------|----------|--------|----------|----------|
| Age (Years) < 50        | 30              | 1 (1.8%)     | 10 (17.9%) | 16 (26.6%) | 3 (5.3%) | 0 (0.0%) | 0.0954   |
| ≥50                     | 26              | 0 (0.0%)     | 4 (7.1%)  | 12 (21.4%) | 9 (16.1%) | 1 (1.8%) |          |
| Sex (n = 56) Male       | 29              | 0 (0.0%)     | 6 (10.7%) | 16 (28.6%) | 6 (10.7%) | 1 (1.8%) | 0.5937   |
| Female                  | 27              | 1 (1.8%)     | 8 (14.3%) | 12 (21.4%) | 6 (10.7%) | 0 (0.0%) |          |
| Oral Lesion (n = 116)   | Ulcer           | 57           | 0 (0.0%)  | 32 (27.6%) | 16 (13.8%) | 8 (6.9%) | 1 (0.8%) | 0.0002   |
| Others                  | 59              | 1 (1.8%)     | 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 predispition 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/0Hm1T6X) 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.

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