Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Oral health conditions and COVID-19: A systematic review and meta-analysis of the current evidence

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ABSTRACT

Background: The coronavirus disease 2019 (COVID-19) pandemic has highlighted the importance of understanding the underlying conditions that lead to COVID-19. Oral health has systemic implications in the maintenance of a healthy state. This study aimed to summarize evidence on the prevalence of oral health conditions in participants with COVID-19 and assess the associations between oral health conditions and COVID-19 related outcomes.
Methods: Article searches were conducted in five databases and the gray literature from December 1, 2019 to March 1, 2021. Studies that reported oral health conditions for participants with COVID-19 and/or examined associations between oral health and COVID-19 were included.
Results: We identified 15 articles that encompassed 5,377 participants with COVID-19 from 10 countries. Dry mouth was the most common oral health condition reported (41.0%), followed by oral lesions (38.8%), orofacial pain (18.3%), and periodontal symptoms (11.7%). Based on the pooled odds ratios (ORs), periodontal symptoms were not associated with COVID-19 positivity (OR = 1.1; 95% confidence intervals [CI], 0.73–1.65) or mortality (OR = 2.71; 95% CI, 0.64–11.51), but were associated with COVID-19 severity (OR = 3.18; 95% CI, 1.81–5.58).
Conclusions: Oral health conditions are common in participants with COVID-19 and should be considered in both the onset and progression of this disease. Knowledge in this area is still limited, and the quality of the data extracted was low. Further longitudinal studies are needed to ascertain whether oral health conditions are a consequence of infection with SARS-CoV-2 or whether they predate infection and are risk factors for COVID-19.

1. Introduction

The human-to-human transmission of novel coronavirus disease 2019 (COVID-19) is a global pandemic. As of March 13, 2021, COVID-19 has affected more than 119 million people globally. COVID-19 is a contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a single-stranded RNA-enveloped virus [1]. A large number of glycosylated spike proteins cover the surface of SARS-CoV-2 and bind to the host cell receptor angiotensin-converting enzyme 2 (ACE2) with subsequent cleavage by the transmembrane protease serine 2 (TMPRSS2) enzyme, mediating viral cell entry [1–4]. The most typical symptoms of COVID-19 cases are fever, cough, headache, fatigue, and slight dyspnea. Other symptoms include dry mouth, sore throat, muscle pain, vomiting, and diarrhea [5]. The oral cavity has been associated with COVID-19, as ACE2 receptor and TMPRSS2 have been identified in the epithelial cells of the oral mucosa [6] and the salivary glands [2,7,8]. Oral health conditions in adults with COVID-19 infection have been documented in multiple countries. A case report from Saudi Arabia described three SARS-CoV-2-infected patients with extensive gingival bleeding [9]. A recent longitudinal study of COVID-19 survivors in Milan, Italy, found that the prevalence of salivary gland ectasia (reflecting a hyperinflammatory response to SARS-CoV-2) and dry mouth among 122 COVID-19 survivors were 43% and 25%, respectively [10]. Nonetheless, it remains uncertain whether these oral health conditions are clinical responses to COVID-19 infections or impaired immune systems, given the possibilities of coinfections with other viruses, bacteria, or fungi, or adverse reactions to medications or treatments [11].

Oral health conditions have systemic implications in the maintenance of a healthy state (symbiosis). Accumulating evidence has demonstrated the associations between oral health conditions and systemic diseases [12,13]. For instance, periodontal disease (PD) is an inflammatory disease that involves a series of diseases states caused by physiologic disruptions to a finely tuned equilibrium that may heighten host inflammatory response [14] and contribute to systemic diseases [15]. SARS-CoV-2 has been identified as a cause of hyperinflammatory state with the release of cytokines from host cells, referred to as “cytokine storm” [16]. Cytokines play a major role in bacterial stimulation and tissue destruction [17] and are thought to underlie the PD and systemic conditions’ associations. A recent systematic review and meta-analysis

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[12] demonstrated moderate to strong associations between periodontitis and respiratory diseases. In addition, the human oral cavity is home to the second most diverse microbial community in the body; more than 700 species of bacteria colonize the hard surfaces of the teeth and the soft tissues of the oral mucosa [18]. Patients suffering from severe PD are considered to have an open wound of approximately 40 cm^2 in the oral cavity [19], "leaving the door wide open" to pathogen such as SARS-CoV-2. Thus, associations between oral health conditions and COVID-19 related outcomes, such as positivity, severity, and mortality, are biologically plausible.

Since the clinical manifestations of COVID-19 beyond pulmonary inflammation are still inadequately known, the oral health conditions associated with COVID-19 remain understudied and underappreciated. The global COVID-19 crisis has highlighted the importance of understanding the underlying conditions that lead to COVID-19 related outcomes, such as positivity, severity, and mortality [20–23]. Accordingly, the objectives of this systematic review were to synthesize all relevant studies to determine the prevalence of oral health conditions in participants with COVID-19 infection and identify the associations of oral health conditions with COVID-19 related outcomes.

2. Methods

2.1. Protocol and registration

We developed a systematic review protocol based upon the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) group [24]. We registered this work with the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42020213809).

2.2. Search strategy

A systematic literature search was performed on five databases: PubMed, EMBASE, Web of Science, Cochrane Library, and CINAHL. Pre-publication manuscripts were retrieved from pre-print servers (Bioxiv and Medrxiv). Google Scholar was searched for relevant grey literature reports (Supplementary Table 1. Search Strategy). Reference lists of all included studies were also searched for potential missed studies. All included database/pre-print servers/Google Scholar platforms were searched from December 1, 2019, to March 1, 2021.

2.3. Eligibility criteria

All studies that reported oral health conditions of participants with COVID-19 infection and/or examined associations between oral health conditions and COVID-19 related outcomes were eligible for this systematic review. The inclusion criteria were defined based on the Population, Exposure, Comparator, and Outcomes (PECO) strategy so that all research studies with human participants were initially considered. Studies that excluded were case reports, reviews, commentaries, editorials, or animal or *in vitro* studies, or where data could not be reliably extracted. No exclusions were made for language or publication status.

2.4. Screening and selection of studies

All identified references were organized and uploaded into Endnote X9 (Thomson Reuters) to remove duplicates. Two reviewers (X.Q. and M.H.) independently screened titles and abstracts according to the eligibility criteria. Studies that met the inclusion criteria were obtained in full. Any discrepancies on the eligibility of articles were resolved by discussion and mutual agreement between the two reviewers. The senior author (B.W.) was involved as needed for the final decision.

2.5. Data extraction

Data extraction was performed independently by two of the authors (X.Q. and M.H.). The essential information that was extracted for the included studies was the name of the first author, year of publication, country of the participating population, study design, sample size, ages of participants, COVID-19 related outcomes, oral health problems and disorders, and methods of evaluating oral health conditions. Studies were grouped by the types of effects they reported and their characteristics, e.g., exposures, outcomes, and evaluation methods. In They were summarized in both a narrative review and a table of results. Any disagreements were resolved by discussion and mutual agreement between the authors.

2.6. Risk of bias within studies

The quality appraisal of each study was independently evaluated by two of the authors (X.Q. and M.H.) using the Newcastle-Ottawa Scale (NOS) for cross-sectional studies, case series, cohort studies, or case-control studies [25]. NOS is a validated tool for assessing the quality of non-randomized studies. The total score of each cross-sectional study ranged from 0 to 5, and cross-sectional studies with a low risk of bias were defined as studies with a NOS score ≥ 3. For case series, retrospective cohort studies, and case-control studies, the total score ranged from 0 to 9, and studies with a NOS score ≥ 6 were regarded as having a low risk of bias [25]. The senior author (B.W.) was consulted in cases when there were disagreements.

2.7. Summary measures

Based on the included studies in this review, oral health conditions were grouped into the dry mouth, oral lesions, periodontal symptoms and diseases, and orofacial pain. Dry mouth was self-rated by study participants. Oral lesions were assessed by their clinical presentations and diagnoses, including ulcerative lesion, blister, erythema multiforme-like lesion, lingual papillitis, aphthous stomatitis, and mucositis. Self-reported oral pain or bleeding gums and loose teeth were used as surrogates for periodontal symptoms [20,22]. Periodontitis was diagnosed according to the respective International Statistical Classification of Diseases and Related Health Problems (ICD) codes [21,23]. Orofacial pain comprised dental/oral pain, jaw/bone/joint pain, trigeminal neuralgia, and facial tingling.

COVID-19 related outcomes were summarized as COVID-19 positivity, severity, and mortality. COVID-19 positivity was determined by reverse transcription-polymerase chain reaction (RT-PCR) test results for SARS-CoV-2 obtained from oropharyngeal/nasopharyngeal swab, cerebrospinal fluid, saliva, or bronchoalveolar lavage. COVID-19 severity was assessed by hospitalization, intensive care unit (ICU) admission, and use of ventilation. Given that the definition of COVID-19 severity differed across studies, we considered non-hospitalized patients to be mild/moderate cases and hospitalized patients to be severe cases. COVID-19 mortality was determined by death following a positive COVID-19 test result.

2.8. Synthesis and statistical analysis

We categorized and compared studies regarding different outcomes by qualitative synthesis. The meta-analyses of the proportions of different outcomes were performed via observational studies using STATA 15 (College Station, TX: StataCorp LLC, 2015). The overall prevalence of dry mouth/oral lesions/periodontal symptoms/orofacial pain in participants with COVID-19 infection was calculated through absolute or relative frequencies and their associated 95% confidence intervals (CIs). The meta-analyses of the associations of periodontal symptoms with COVID-19 positivity, severity, and mortality were also generated using STATA.

The outcomes were measured using the dichotomous analysis of odds ratios (ORs) and their associated 95% CIs. The I^2 test was used to calculate statistical heterogeneity, which determined whether a fixed ($I^2 < 50\%$) or random ($I^2 \geq 50\%$) effects model should be applied [26]. Subgroup analysis was conducted if heterogeneity was detected by the method of ascertainment. For instance, subgroup analysis was performed for studies using clinical examination vs. self-reported survey/questionnaire to ascertain oral health conditions. Subgroup analysis was not performed if there were insufficient studies across subgroups.

2.9. Certainty of evidence

The Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) [27] rating were used to assess the quality of evidence and recommendation strength for all included studies. The certainty of the evidence was rated for the prevalence of oral health conditions and their associations with COVID-19 positivity, severity, and mortality. In GRADE, the body of evidence from observational studies is initially set as low certainty (vs. randomized trials, where it is initially set as high certainty) [27]. This assessment is based on the risk of bias, inconsistency, indirectness, imprecision, and other considerations. Evidence quality was characterized as high, moderate, low, or very low [27].

3. Results

3.1. Characteristics of included studies

We retrieved 9333 records from all databases. After removing duplicates, screening records, and full-text review, 15 studies were selected for quantitative synthesis. A flowchart detailing this process is presented in Fig. 1 and the characteristics of included studies were summarized in Table 1. A total of 5377 participants with COVID-19 infection were included in this review, and individual sample sizes for the studies ranged from 9 to 1616 COVID-19 cases. The 15 included studies were distributed across 10 countries: 5 in Italy [10,28–30], 2 in Egypt [20,31], 1 in the U.S [21]., 1 in Israel [32], 1 in China [33], 1 in Turkey [34], 1 in Slovakia [35], 1 in Spain [36], 1 in the U.K [22]., and 1 in Qatar [23]. All studies employed RT-PCR testing to detect viral RNA to confirm COVID-19 infection. For research design, 5 are cross-sectional studies [31,31,33,34,36], 5 are case series [28–30,32,35], 3 are retrospective cohort studies [10,22,37], and 2 are case-control studies [21,23]. Eight studies assessed oral health problems and conditions using self-reported surveys, 6 used clinical extraoral and intraoral examinations, and 1 used electronic health records.

3.2. Risk of bias within studies

The assessment of the risk of bias for each study is summarized in Table 1 and detailed in Supplementary Table 2. Case series and cohort, case-control, and cross-sectional studies were evaluated with the appropriate checklist for each study design [25]. Appraisal of these studies found a high risk of selection bias due to their retrospective designs, lack of representativeness due to non-random sampling, and low response rates of participants with COVID-19 infection. Six studies demonstrated a low risk of bias because both surveys and clinical examinations were administered to participants with COVID-19 infection and the studied groups were comparable with respect to age. There was also a risk of recall bias if the surveys were distributed after participants were discharged from hospitals because they may not be able to accurately recall the oral health conditions they experienced and/or the time their symptoms last [38].

3.3. Prevalence of oral health conditions

3.3.1. Dry mouth

Dry mouth was assessed by asking participants whether they complained of xerostomia/dry mouth while infected with COVID-19 [10,29–33,37]. A total of 1123 participants with COVID-19 infection were identified for evaluation of dry mouth. Of these, 499 exhibited some level of dry mouth. The overall prevalence of dry mouth in participants with COVID-19 infection was 41.0% (95% CI, 33.0%–48.9%; Fig. 2A), using random-effect estimation ($I^2 = 83.1\%$, $P < 0.001$). As shown in Fig. 2A, the pooled prevalence is represented by the diamond shape, individual study estimates are represented by square shapes, and horizontal lines represent their 95% CIs.

3.3.2. Oral lesions

Overall, 419 of 1707 participants with COVID-19 infection were reported to have oral lesions that varied in concerning location, structure, color, and pain score. The types of oral lesions identified in the 7 studies included ulcerative lesion ($n = 240$), blister ($n = 19$), erythema multiforme-like lesion ($n = 26$), petechiae ($n = 14$), lingual papillitis ($n = 33$), aphthous stomatitis ($n = 27$), and mucositis ($n = 22$) [10,28,31,32,34–36], where n refers to the number of participants with each oral health condition. Participants with oral lesions identified prior to COVID-19 diagnosis were excluded in 3 studies [31,32,34]. A meta-analysis using a random-effects model ($I^2 = 97.9\%$, $P < 0.001$) of included studies yielded a 38.8% prevalence of oral lesions among participants with COVID-19 infection (95% CI, 23.9%–53.6%; Fig. 2B).

3.3.3. Periodontal symptoms and diseases

Of 2349 participants with COVID-19 infection in 4 included studies [22,30–32], 348 reported periodontal signs or symptoms. Periodontal symptoms included bleeding gums, painful gums, and loose teeth. Two studies [22,30] excluded patients with self-reported histories of PD or who had experienced periodontal symptoms prior to the COVID-19 pandemic, and 1 study [31] also excluded patients with poor oral hygiene before the pandemic. A meta-analysis using a random-effects model yielded an 11.7% prevalence of periodontal symptoms (95% CI, 4.9%–18.5%). Heterogeneity was detected with an I^2 of 94.1% ($P < 0.001$), confirming the use of the random effects model (Fig. 2C).

3.3.4. Orofacial pain

A total of 835 participants with COVID-19 infection from 3 studies [10,31,32] were evaluated for orofacial pain. Of these, 196 reported orofacial pain included dental/oral pain, jaw/bone/joint pain, trigeminal neuralgia, or facial tingling. The reported prevalence of orofacial pain in individual studies ranged from 12.9% to 28.3%. Using random-effect estimation ($I^2 = 93.3\%$, $P < 0.001$), the overall prevalence of orofacial pain in participants with COVID-19 infection is 18.3% (95% CI, 7.1%–29.4%; Fig. 2D).

3.4. Associations between periodontal symptoms and COVID-19 related outcomes

Four studies examined the association of periodontal symptoms with COVID-19 positivity, severity, and mortality [20–23]. The pooled OR from 2 studies [21,22] yielded no meaningful association between periodontal symptoms and COVID-19 positivity (OR = 1.10; 95% CI, 0.73–1.65; $I^2 = 0\%$, $P = 0.950$; Fig. 3A). Regarding COVID-19 severity, 3 studies linked periodontal symptoms with a higher rate of hospitalization [22], ICU admission [20,23], and use of assisted ventilation [20,23]. Specifically, COVID-19 patients with painful or bleeding gums had a higher risk of mortality (OR = 1.71; 95% CI: 1.05–2.72) but not hospital admission (OR = 0.90; 95% CI: 0.59–1.37), but patients with loose teeth did not have a higher risk of hospital admission or mortality compared to the control group (OR = 1.55, 95% CI: 0.87–2.77; OR = 1.85,

Table 1
Descriptive characteristics of Studies (n = 15).

Author, Country, Year	Study Design	Sample and setting, n	Age, y, Mean ± SD or Median (Range)	COVID-19 Positivity, n (%)	COVID-19 Severity, n (%)	Oral Health Conditions (measurement), n (%)	Method of Evaluating Oral Health Conditions	Risk of Bias
AbuBakr [31], Egypt, 2021	Cross-sectional study	573 recovered COVID-19 mild-to-moderate cases	36 (19–50)	573 (100)	NR	Orofacial pain (dental/oral pian, jaw/bone/joint pain): 162 (28.3) Oral lesions (ulceration): 117 (20.4) Dry mouth: 273 (47.6) Periodontal symptoms (halitosis): 60 (10.5)	Self-report survey	Low
Biadsee [32], Israel, 2020	Retrospective case series	140 ambulatory, non-hospitalized COVID-19 patients	36 (18–73)	140 (100)	NR	Dry mouth: 72 (51.4) Oral lesions (ulcerative lesion): 49 (35.0) Periodontal symptoms (gum bleeding): 6 (4.3) Orofacial pain: 18 (26)	Self-report survey	Low
Chen [33], China, 2020	Cross-sectional study	108 non-hospitalized COVID-19 patients	52 (20–81)	108 (100)	NR	Dry mouth: 50 (46.3)	Self-report survey	High
Fantozzi [37], Italy, 2020	Retrospective cohort series	111 COVID-19 patients evaluated at Emergency Department	57 (48–67)	111 (100)	Transferred to ICU: 6 (5.4)	Dry mouth: 51 (45.9)	Self-report survey	High
Favia [28], Italy, 2021	Retrospective case series	123 non-hospitalized COVID-19 patients	72 (51–91)	123 (100)	NR	Oral lesions (ulcerative lesion [n = 22], blister [n = 19], erythema multiforme-like lesion [n = 7], petechiae [n = 14]): 65 (52.8)	Clinical examination	High
Fidan [34], Turkey, 2021	Cross-sectional study	74 non-hospitalized COVID-19 patients	42 (19–78)	74 (100)	NR	Oral lesions (aphthous-like ulcer [n = 27], erythema [n = 19], mucositis [n = 12]): 58 (78.4)	Clinical examination	High
Freni [29], Italy, 2020	Retrospective case series	50 non-hospitalized COVID-19 patients	38 (18–65)	50 (100)	NR	Dry mouth: 17 (34)	Self-report survey	High
Gherlone [10], Italy, 2021	Retrospective cohort series	122 COVID-19 survivors that were hospitalized before	62.5 ± 9.0	122 (100)	Hospitalized: 115 (94.3) Transferred to ICU: 30 (24.6) Noninvasive ventilation: 54 (44.3)	Salivary gland ectasia: 46 (38), Dry mouth: 30 (24.6), Abnormalities in TMJ: 9 (7.4), Masticatory muscle weakness: 22 (18.0), Oral lesions (ulcer): 49 (40.2), Orofacial pain (trigeminal neuralgia, facial tingling): 16 (13.1)	Clinical examination	Low
Hocková [35], Slovakia, 2021	Retrospective case series	9 COVID-19 patients at ICU	64 (61–68)	9 (100)	NR	Oral lesions (ulcers): 3 (33.3)	Clinical examination	High
Kamel [20], Egypt, 2021	Cross-sectional study	308 non-hospitalized COVID-19 patients	35.0 ± 8.1	308 (100)	Hospitalized patients who required oxygen or ICU admission: 80 (26.0), Mild cases: 228 (74.0)	Self-rated oral health status: poor = 64 (20.8); fair = 166 (53.9); good = 78 (25.3)	Self-report survey	Low
Katz [21], US, 2020	Case-control study	987, 849 inpatients and outpatients attending health centers in Florida, US	NR	889 (0.09)	NR	Periapical dental infection: 16 (1.7) in COVID-19 patients Periodontal disease: 7 (0.77) in COVID-19 patients Caries: 31 (3.48) in COVID-19 patients	Electronic records (EPIC)	High
Larvin [22], UK, 2020	Retrospective cohort study	13,502 participants tested for COVID-19	68.6 ± 8.4	1,616 (10.5)	Hospital admission: 4,083 (30.2) Mortality: 644 (4.8)	Periodontal diseases: Bleeding gums: 1,329 (8.7) of all participants, 181 (11.2) of COVID-19 patients Painful gums: 365 (2.4) of all participants, 44 (2.7) of COVID-19 patients Loose teeth: 406 (2.7) of all participants, 53 (3.3) of COVID-19 patients	Self-report survey	Low
Marouf [23], Qatar, 2021	Case-control study	568 COVID-19 patients	42.4 ± 12.1	568 (100)	ICU admission: 36 (6.3) Assisted ventilation: 20 (3.5) Death: 14 (2.5)	Periodontitis: 258 (45.4)	Clinical examination	Low
Nuno-Gonzalez [36], Spain, 2021	Cross-sectional study	666 non-hospitalized COVID-19 patients	55.7 ± 11.1	666 (100)	NR	Oral lesions (lingual papillitis [n = 35], aphthous stomatitis [n = 33], mucositis [n = 10]): 78 (11.7)	Clinical examination	High
Sinjari [30], Italy, 2020	Retrospective case series	20 hospitalized COVID-19 patients	69.2 ± 19.0	20 (100)	NR	Dry mouth: 6 (30) Periodontal symptoms (bleeding of gums): 4 (25)	Self-report survey	High

Note: NR = Not Reported; COVID-19 = Coronavirus Disease 2019; ICU = Intensive Care Unit.

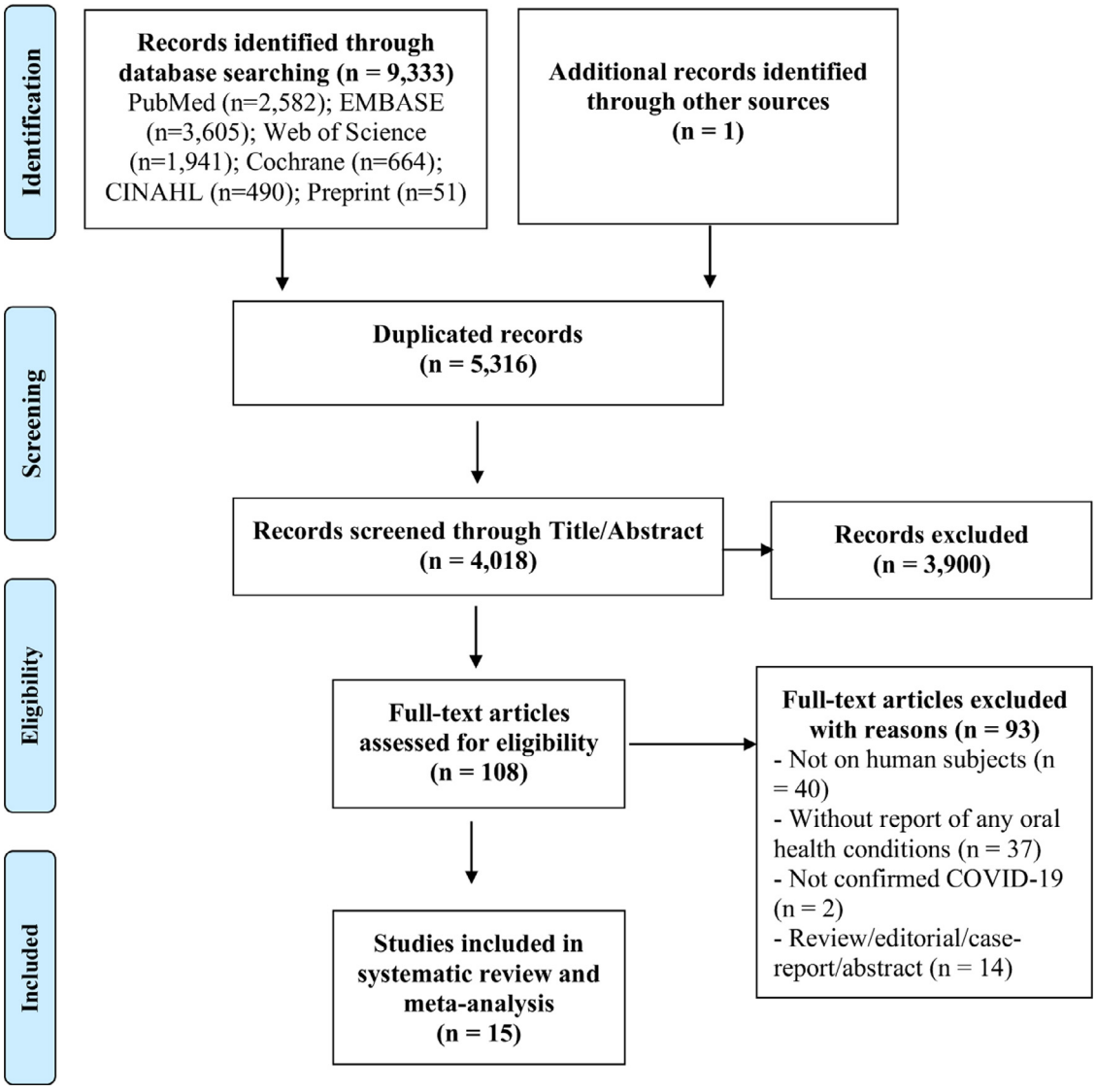

Fig. 1. PRISMA flowchart of study selection process.

95% CI: 0.92–2.72) [22]. Overall, an association was observed between periodontal symptoms and mild/moderate COVID-19 as compared to severe COVID-19 (OR = 3.18; 95% CI, 1.81–5.58; I^2 = 26.5%, P = 0.256; Fig. 3B). In contrast, 2 studies examined the link between periodontal symptoms and COVID-19 mortality [22,23] and found no significant association (OR = 2.71; 95% CI, 0.64–11.51; I^2 = 51.9%, P = 0.149; Fig. 3C).

3.5. Subgroup analysis by the method of ascertainment

Analysis of only those studies that used self-reported surveys [31,32] to ascertain the presence of oral lesions found a 27.2% prevalence among 713 participants with COVID-19 infection (95% CI, 13.0%–41.5%; I^2 = 91.0%, P < 0.001). Analysis of only those studies that used clinical examinations [10,28,34–36] to ascertain the presence of oral lesions found a 43.5% prevalence among 994 participants with COVID-19 infection (95% CI, 14.8%–72.2%; I^2 = 98.5%, P < 0.001). Forest plots are provided in Fig. 2B. No subgroup analyses were performed with the respect to other oral health conditions, as only a single study used both clinical examinations and self-reported surveys to ascertain oral health conditions.

3.6. Certainty of evidence

Using the GRADE system, the certainty of the evidence was very low for the prevalence of all examined oral health conditions in participants with COVID-19 infection and the association of periodontal symptoms with COVID-19 positivity and mortality. The certainty of the evidence was marginally better at low for the association between periodontal symptoms and COVID-19 severity (Supplementary Table 3).

4. Discussion

To our knowledge, this is the first systematic review to summarize the current evidence on the prevalence of oral health conditions in participants with COVID-19 infection and their associations with COVID-19 positivity, severity, and mortality. Dry mouth is the most common oral health condition in participants with COVID-19 infection, with a prevalence of 41.0%, followed by oral lesions (38.8%), orofacial pain (18.3%), and periodontal symptoms (11.7%). Moreover, periodontal symptoms are associated with COVID-19 severity but not with COVID-19 positivity or mortality.

Documented COVID-19 cases have been associated with dry mouth, oral lesions, and periodontal symptoms in the scientific literature

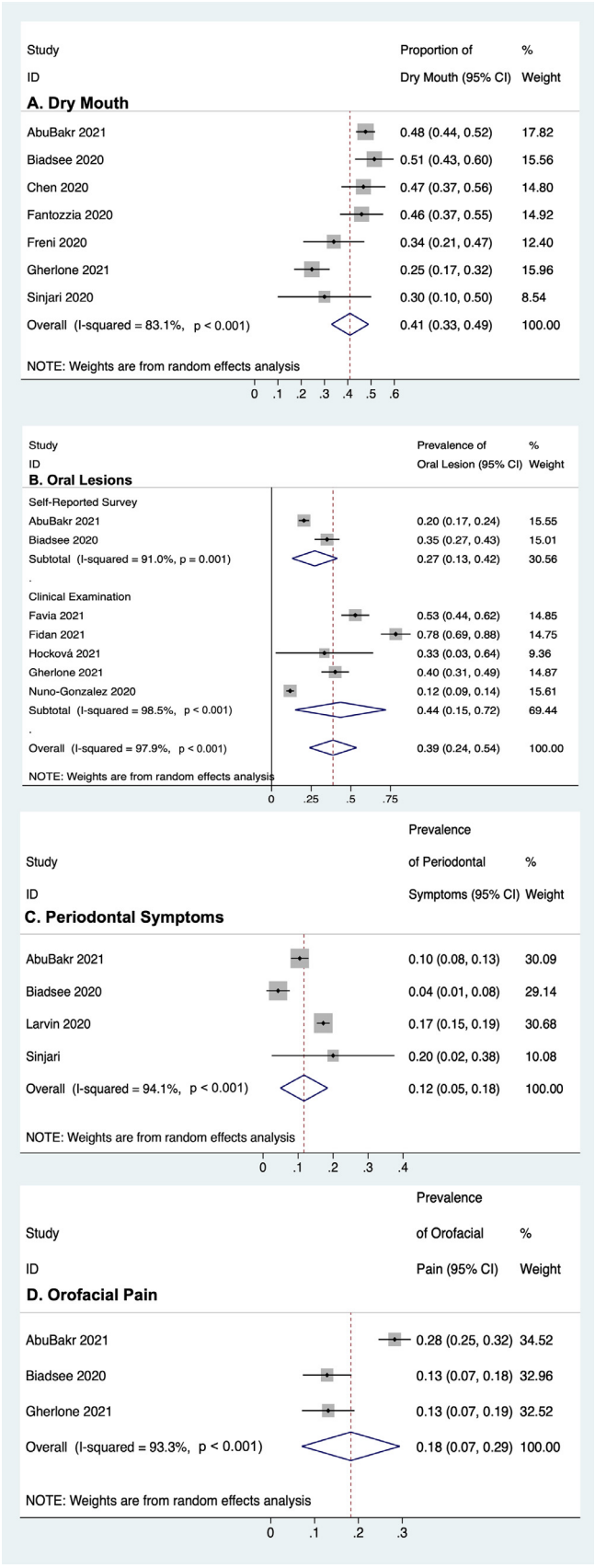

Fig. 2. A. Prevalence of dry mouth in participants with COVID-19 infection, Fig. 2B. Prevalence of oral lesions in participants with COVID-19 infection, Fig. 2C. Prevalence of periodontal symptoms in participants with COVID-19 infection, Fig. 2D. Prevalence of orofacial pain in participants with COVID-19 infection.

[10,31,32,37]. The oral cavity cells have viral entry receptor ACE-2 that allows viral replication and may cause the inflammation and destruction of oral tissue [39]. Recent studies [6–8] have suggested that the oral cavity is at potentially high susceptibility to COVID-19 infection because of the existence of ACE2 receptor and TMPRSS2 in the epithelial cells of the oral mucosa [6] and the salivary glands [2,7,8]. A post-mortem study of 7 people who died of COVID-19 found the presence of SARS-CoV-2 in periodontal tissue [40]. Histopathologic analyses identified morphologic alterations in the keratinocytes of junctional epithelium, vacuolization of the cytoplasm, and nucleus and nuclear pleomorphism [40]. The distribution of ACE2 receptors may help determine the route of SARS-CoV-2 infection. The presence of ACE2 receptors on the oral mucous membrane and salivary glands may be involved in COVID-19 infection and subsequent dysfunction. The interaction between SARS-CoV-2 and ACE2 and the subsequent cleavage by TMPRSS2 enzyme might disrupt the function of oral keratinocytes and the epithelial lining of the salivary gland ducts [41], which holds the potential of resulting in oral health conditions [42].

The included studies provide evidence that the onset of oral health conditions may be directly associated with COVID-19 infection. However, oral health conditions could be the consequence of many factors, such as COVID-19 related stress and/or emotional response, intubation, medication, and immune-disorders [42–44]. Hence, whether or not the identified oral health conditions are directly caused by SARS-CoV-2 or are associated manifestations resulting from antibiotic treatment or the severely compromised immunity of COVID-19 infection remains to be determined [42–44]. It is speculated that oral lesions may indicate persisting immunological storm-related damage after SARS-CoV-2 eradication, and may be further exacerbated by an upregulation in inflammatory markers due to the SARS-CoV-2 [42]. Antibiotic treatment has been frequently used as both a preventive and therapeutic measure in severe COVID-19 patients. The favorable outcomes indicate the potential coinfection of SARS-CoV-2 and other infectious agents in the oral cavity. Therefore, oral microbiome rearrangement following antibiotic treatment may predispose patients to the development of oral health conditions [10], although causality may be challenging to confirm. Future studies are needed to elucidate the connection between COVID-19 infection and oral health conditions, considering the pathogenesis and direct action of SARS-COV-2, the effect of the inflammatory response on oral homeostasis, and the impact of antibiotic or other treatments.

This review did not find meaningful associations between periodontal symptoms and COVID-19 positivity and mortality, likely due to the small number of studies included. Appraisal of these studies demonstrated a high risk of selection bias because of their retrospective designs, non-probability sampling methods, and lack of representativeness and control populations. In 3 included studies that measured the association between periodontal symptoms and COVID-19 positivity and mortality [20,22,23], there was a high risk of measurement bias since 1 study used a self-reported survey [22]. The inconsistency in methods likely reflects the costs and difficulties of performing oral health evaluations due to the novelty and intensity of the COVID-19 pandemic during the periods when the studies were conducted.

In contrast, a significant association was found between periodontal symptoms and COVID-19 severity, which has been linked to immune dysregulation, potentially leading to a cytokine storm found to cause thrombosis and multi-organ failure involving the brain, heart, and kidneys [17,45]. Although the effect of periodontal symptoms in participants with COVID-19 infection is not well understood, several hypotheses have been proposed. A recent review examined the potential role of cytokines in COVID-19 severity [46]. Note that periodontal symptoms can increase the levels of interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factors (TNF), which have been implicated as major interferons leading to a cytokine storm [47]. Anti-inflammatory therapeutic treatments such as corticosteroids, IL-6 inhibitors, and monoclonal antibody drugs have been used to treat patients with COVID-19 [48]. In addition to common inflammatory pathways, a recent review

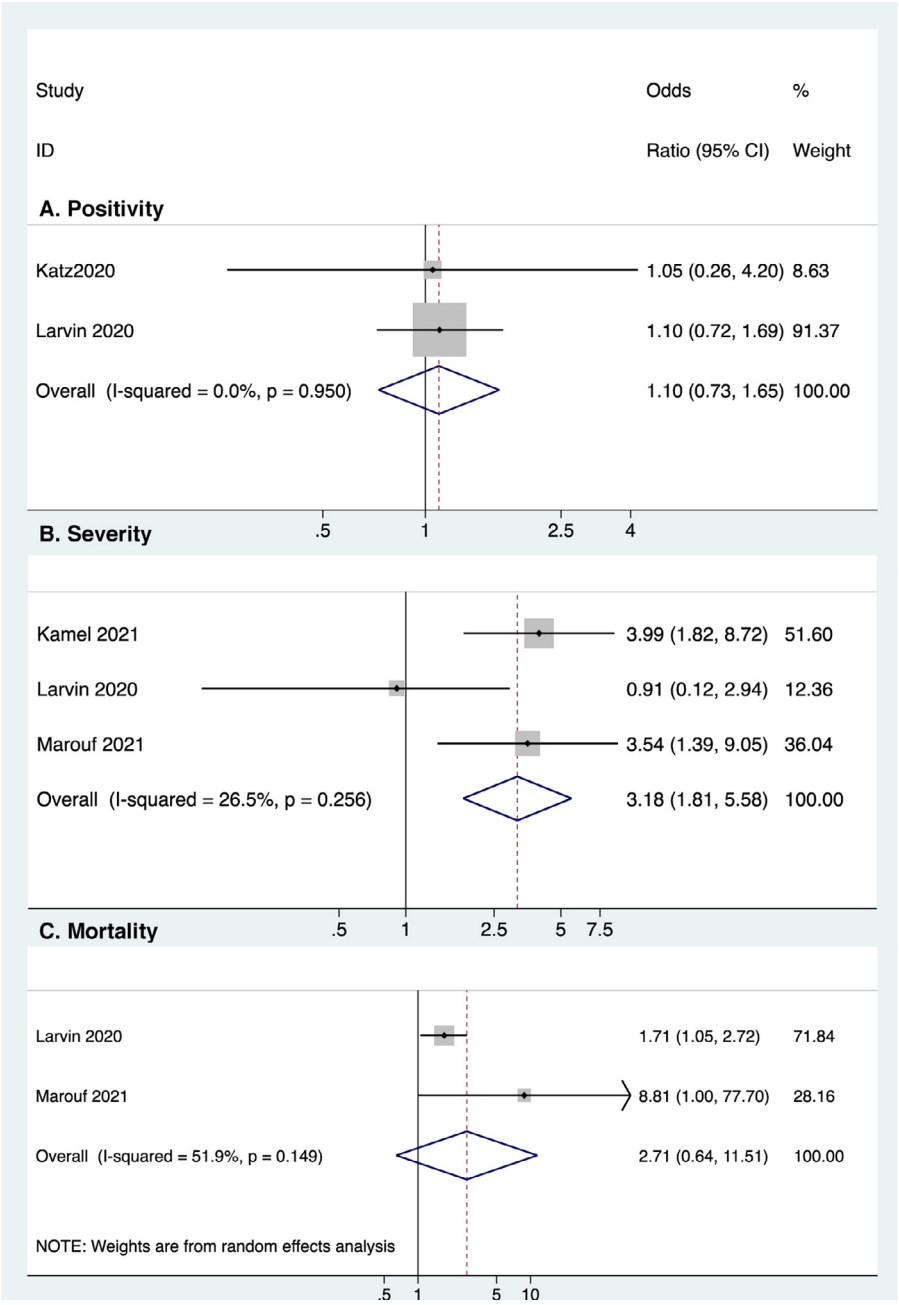

Fig. 3. Association between periodontal symptoms with COVID-19 positivity (A), severity (B), and mortality (C).

has suggested that oral disease may exacerbate COVID-19 severity via two additional mechanisms [42]. First, periodontopathic bacteria have been implicated in aspirational pneumonia and an increase in viral respiratory infections [49]. Second, age could be partially responsible for the connection between PD and COVID-19, since oral health conditions that affect older adults share common risk factors with PD such as poor oral hygiene, longtime medication use, and co-occurring chronic diseases [50], and old adults aged 65 years and older represent a high-risk group for COVID-19 severity due to potential chronic comorbidities and weakened immune systems [44].

Several limitations of this review need to be acknowledged. First, most of the studies did not report the presence of SARS-CoV-2 in the participants' oral cavities. In future research, the characterization of the oral manifestations of COVID-19 in infected individuals may consider including incisional biopsy, followed by direct viral testing for SARS-CoV-2, to distinguish between features related to the local viral persistence and those related to the sequelae of the infection. Second, none of the included studies reported other viral, bacterial, and fungal coinfections in participants with COVID-19 infection. A national consensus in Spain found that a divergent mucosal lesion pattern is related to multiple viruses [51], and bacterial and fungal coinfections are common in severe COVID-19 cases. Admitted COVID-19 patients frequently receive antibiotics, but no information on bacterial/fungal sensitivity was provided in the reviewed studies [11]. Future research is needed to investigate coinfections in severe COVID-19 cases and examine the causes of oral health conditions in participants with COVID-19 infection. Third, only 6 studies collected information on oral health conditions by clinical examinations in the current research, as most of the dental and university clinics were closed at the time of these investigations or treating only emergency cases. Hence, in terms of dry mouth and periodontal symptoms, subjective methods such as surveys were almost exclusively used, which may not accurately diagnose these con-

ditions. Future large cohort studies with validated measurement tools or clinical examinations are needed to better understand the relationships between oral health conditions and COVID-19. Fourth, although the included studies controlled for confounding factors such as smoking, comorbidities, and individual characteristics such as age, sex, and education, the systematic review may contain inherent estimation biases due to the retrospective nature of the study designs and the heterogeneity in the age/race/sex/education of the participants analyzed. Finally, further studies are needed to elucidate the connection between COVID-19 infection and oral health conditions. The direct action of the virus, the effect of the inflammatory response on oral homeostasis, neurological mechanisms, and the impact of treatments/medication, should all be considered.

5. Conclusion

Findings from this study suggest that dry mouth was the most prevalent oral health condition (41%), followed by oral lesions (38.8%), orofacial pain (18.3%), and periodontal symptoms (11.7%). We also found that periodontal symptoms are associated with COVID-19 severity. The findings of this systematic review indicate that oral health conditions may be common in people with COVID-19 infection and should be considered in both the onset and progression of the disease. However, knowledge in this area is still limited, and the quality of the data extracted was low. Further longitudinal studies are needed to ascertain whether dry mouth, orofacial pain and periodontal symptoms are a consequence of infection with SARS-CoV-2 or whether they predate infection and are risk factors for COVID-19.

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Declaration of Competing Interest

The authors declare that they have no financial interests or personal relationships that could influence the work reported in this study.

CRediT authorship contribution statement

Xiang Qi: Visualization, Data curation, Writing – original draft. **Mary E. Northridge:** Visualization, Writing – original draft. **Mengyao Hu:** Data curation. **Bei Wu:** Conceptualization, Visualization, Writing – original draft.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahr.2022.100064.

References

[1] Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med 2020;46:586–90. doi:10.1007/s00134-020-05985-9.
[2] Huang N, Pérez P, Kato T, Mikami Y, Okuda K, Gilmore RC, et al. SARS-CoV-2 infection of the oral cavity and saliva. Nat Med 2021. doi:10.1038/s41591-021-01296-8.
[3] Usami Y, Hirose K, Okumura M, Toyosawa S, Sakai T. Brief communication: immunohistochemical detection of ACE2 in human salivary gland. Oral Sci Int 2020 osi2.1085. doi:10.1002/osi2.1085.
[4] V'kovski P, Kratzel A, Steiner S, Stalder H, Thiel V. Coronavirus biology and replication: implications for SARS-CoV-2. Nat Rev Microbiol 2021;19:155–70. doi:10.1038/s41579-020-00468-6.
[5] Singh A, Purohit BM, Taneja S. Loneliness and disability as predictors of oral diseases among 2 groups of older adults in central India. J Am Dent Assoc 2020;151:427–37. doi:10.1016/j.adaj.2020.02.017.
[6] Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci 2020;12:8. doi:10.1038/s41368-020-0074-x.
[7] Pascolo L, Zupin L, Melato M, Tricarico PM, Crovella S. TMPRSS2 and ACE2 Co-expression in SARS-CoV-2 Salivary Glands Infection. J Dent Res 2020;99:1120–1. doi:10.1177/0022034520933589.
[8] Xu J, Li Y, Gan F, Du Y, Yao Y. Salivary glands: Potential reservoirs for COVID-19 asymptomatic infection. J Dent Res 2020;99 989–989. doi:10.1177/0022034520918518.
[9] Manzalawi R, Alhmamey K, Abdelrasoul M. Gingival bleeding associated with COVID-19 infection. Clin Case Rep 2021;9:294–7. doi:10.1002/ccr3.3519.
[10] Gherlone EF, Polizzi E, Tetè G, De Lorenzo R, Magnaghi C, Rovere Querini P, et al. Frequent and persistent salivary gland ectasia and oral disease after COVID-19. J Dent Res 2021:002203452199711. doi:10.1177/0022034521997112.
[11] Cox MJ, Loman N, Bogaert D, O'Grady J. Co-infections: potentially lethal and unexplored in COVID-19. Lancet Microbe 2020;1:e11. doi:10.1016/S2666-5247(20)30009-4.
[12] Gomes-Filho IS, Cruz SS, Trindade SC, Passos-Soares JdS, Carvalho-Filho PC, Figueiredo A, et al. Periodontitis and respiratory diseases: a systematic review with meta-analysis. Oral Dis 2020;26:439–46. doi:10.1111/odi.13228.
[13] Qi X, Zhu Z, Plassman BL, Wu B. Dose-response meta-analysis on tooth loss with the risk of cognitive impairment and dementia. J Am Med Dir Assoc 2021;22:2039–45. doi:10.1016/j.jamda.2021.05.009.
[14] Winning L, Linden GJ. Periodontitis and systemic disease. BDJ Team 2015;2:15163. doi:10.1038/bdjteam.2015.163.
[15] Fowler EB, Breault LG, Cuenin MF. Periodontal disease and its association with systemic disease. Mil Med 2001;166:85–9. doi:10.1093/milmed/166.1.85.
[16] Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol 2020;20:363–74. doi:10.1038/s41577-020-0311-8.
[17] Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. Lancet Respir Med 2020;8:e46–7. doi:10.1016/S2213-2600(20)30216-2.
[18] Gao L, Xu T, Huang G, Jiang S, Gu Y, Chen F. Oral microbiomes: more and more importance in oral cavity and whole body. Protein Cell 2018;9:488–500. doi:10.1007/s13238-018-0548-1.
[19] Nesse W, Abbas F, van der Ploeg I, Spijkervet FKL, Dijkstra PU, Vissink A. Periodontal inflamed surface area: quantifying inflammatory burden. J Clin Periodontol 2008;35:668–73. doi:10.1111/j.1600-051X.2008.01249.x.
[20] Kamel AHM, Basuoni A, Salem ZA, AbuBakr N. The impact of oral health status on COVID-19 severity, recovery period and C-reactive protein values. Br Dent J 2021. doi:10.1038/s41415-021-2656-1.
[21] Katz J, Yue S, Xue W. Dental diseases are associated with increased odds ratio for coronavirus disease 19. Oral Dis 2020 odi.13653. doi:10.1111/odi.13653.
[22] Larvin H, Wilmott S, Wu J, Kang J. The impact of periodontal disease on hospital admission and mortality during COVID-19 pandemic. Front Med 2020;7:604980. doi:10.3389/fmed.2020.604980.
[23] Marouf N, Cai W, Said KN, Daas H, Diab H, Chinta VR, et al. Association between periodontitis and severity of COVID-19 infection: a case–control study. J Clin Periodontol 2021 jcpe.13435. doi:10.1111/jcpe.13435.
[24] Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097. doi:10.1371/journal.pmed.1000097.
[25] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–5. https://doi.org/10.1007/s10654-010-9491-z.
[26] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane handbook for systematic reviews of interventions. John Wiley & Sons; 2019.
[27] Murad MH, Mustafa RA, Schünemann HJ, Sultan S, Santesso N. Rating the certainty in evidence in the absence of a single estimate of effect. Evid Based Med 2017;22:85–7. doi:10.1136/ebmed-2017-110668.
[28] Favia G, Tempesta A, Barile G, Brienza N, Capodiferro S, Vestito MC, et al. Covid-19 symptomatic patients with oral lesions: clinical and histopathological study on 123 cases of the university hospital policlinic of bari with a purpose of a new classification. J Clin Med 2021;10:757. doi:10.3390/jcm10040757.
[29] Freni F, Meduri A, Gazia F, Nicastro V, Galletti C, Aragona P, et al. Symptomatology in head and neck district in coronavirus disease (COVID-19): a possible neuroinvasive action of SARS-CoV-2. Am J Otolaryngol 2020;41:102612. doi:10.1016/j.amjoto.2020.102612.
[30] Sinjari B, D'Ardes D, Santilli M, Rexhepi I, D'Addazio G, Di Carlo P, et al. SARS-CoV-2 and oral manifestation: an observational, human study. J Clin Med 2020;9:3218. doi:10.3390/jcm9103218.
[31] AbuBakr N, Salem Z, Kamel A. Oral manifestations in mild-to-moderate cases of COVID-19 viral infection in the adult population. Dent Med Probl 2021;58 0–0. doi:10.17219/dmp/130814.
[32] Biadsee A, Biadsee A, Kassem F, Dagan O, Masarwa S, Ormianer Z. Olfactory and oral manifestations of COVID-19: sex-related symptoms-a potential path-

way to early diagnosis. Otolaryngol Neck Surg 2020;163:722–8. doi:10.1177/0194599820934380.
[33] Chen L, Zhao J, Peng J, Li X, Deng X, Geng Z, et al. Detection of SARS-CoV-2 in saliva and characterization of oral symptoms in COVID-19 patients. Cell Prolif 2020;53. doi:10.1111/cpr.12923.
[34] Fidan V, Koyuncu H, Akin O. Oral lesions in Covid 19 positive patients. Am J Otolaryngol 2021;42:102905. doi:10.1016/j.amjoto.2021.102905.
[35] Hocková B, Riad A, Valky J, Šulajová Z, Stebel A, Slávik R, et al. Oral complications of ICU patients with COVID-19: case-series and review of two hundred ten cases. J Clin Med 2021;10:581. doi:10.3390/jcm10040581.
[36] Nuno-Gonzalez A, Martin-Carrillo P, Magaletsky K, Martin Rios MD, Herranz Mañas C, Artigas Almazan J, et al. Prevalence of mucocutaneous manifestations in 666 patients with COVID-19 in a field hospital in Spain: oral and palmoplantar findings. Br J Dermatol 2021;184:184–5. doi:10.1111/bjd.19564.
[37] Fantozzi PJ, Pampena E, Di Vanna D, Pellegrino E, Corbi D, Mammucari S, et al. Xerostomia, gustatory and olfactory dysfunctions in patients with COVID-19. Am J Otolaryngol 2020;41:102721. doi:10.1016/j.amjoto.2020.102721.
[38] Coughlin SS. Recall bias in epidemiologic studies. J Clin Epidemiol 1990;43:87–91. doi:10.1016/0895-4356(90)90060-3.
[39] Brandini DA, Takamiya AS, Thakkar P, Schaller S, Rahat R, Naqvi AR. Covid-19 and oral diseases: crosstalk, synergy or association? Rev Med Virol 2021 rmv.2226. doi:10.1002/rmv.2226.
[40] Fernandes Matuck B, Dolhnikoff M, Maia GVA, Isaac Sendyk D, Zarpellon A, Costa Gomes S, et al. Periodontal tissues are targets for Sars-Cov-2: a post-mortem study. J Oral Microbiol 2021;13:1848135. doi:10.1080/20002297.2020.1848135.
[41] Morris G, Bortolasci CC, Puri BK, Olive L, Marx W, O'Neil A, et al. The pathophysiology of SARS-CoV-2: a suggested model and therapeutic approach. Life Sci 2020;258:118166. doi:10.1016/j.lfs.2020.118166.
[42] Sampson V, Kamona N, Sampson A. Could there be a link between oral hygiene and the severity of SARS-CoV-2 infections? Br Dent J 2020;228:971–5. doi:10.1038/s41415-020-1747-8.
[43] Amorim dos Santos J, Normando AGC, Carvalho da Silva RL, De Paula RM, Cembranel AC, Santos-Silva AR, et al. Oral mucosal lesions in a COVID-19 patient: new signs or secondary manifestations? Int J Infect Dis 2020;97:326–8. doi:10.1016/j.ijid.2020.06.012.
[44] Mo P, Xing Y, Xiao Y, Deng L, Zhao Q, Wang H, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. Clin Infect Dis 2020:ciaa270. doi:10.1093/cid/ciaa270.
[45] Rapkiewicz AV, Mai X, Carsons SE, Pittaluga S, Kleiner DE, Berger JS, et al. Megakaryocytes and platelet-fibrin thrombi characterize multi-organ thrombosis at autopsy in COVID-19: a case series. EClinicalMedicine 2020;24:100434. doi:10.1016/j.eclinm.2020.100434.
[46] Molayem S, Pontes C. The mouth-COVID connection: Il-6 levels in periodontal disease -potential role in COVID-19-related respiratory complications. J Calif Dent Assoc 2020 (epub ahead of print). doi:10.35481/jcda-48-10-01.
[47] Tanaka T, Narazaki M, Kishimoto T. Immunotherapeutic implications of IL-6 blockade for cytokine storm. Immunotherapy 2016;8:959–70. doi:10.2217/imt-2016-0020.
[48] Jahanshahlu L, Rezaei N. Monoclonal antibody as a potential anti-COVID-19. Biomed Pharmacother 2020;129:110337. doi:10.1016/j.biopha.2020.110337.
[49] Okuda K, Kimizuka R, Abe S, Kato T, Ishihara K. Involvement of periodontopathic anaerobes in aspiration pneumonia. J Periodontol 2005;76:2154–60. doi:10.1902/jop.2005.76.11-S.2154.
[50] Müller F, Shimazaki Y, Kahabuka F, Schimmel M. Oral health for an ageing population: the importance of a natural dentition in older adults. Int Dent J 2017;67:7–13. doi:10.1111/idj.12329.
[51] Galván Casas C, Català A, Carretero Hernández G, Rodríguez-Jiménez P, Fernández-Nieto D, Rodríguez-Villa Lario A, et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. Br J Dermatol 2020;183:71–7. doi:10.1111/bjd.19163.