Association Between Periodontal Disease and the Risk of COVID-19 Complications and Mortality: A Systematic Review

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Aim: The COVID-19 pandemic has strained the world’s healthcare systems. Studies have identified how the COVID-19 infections are linked to several co-morbidities such as hypertension, diabetes, cardiovascular disease, renal and pulmonary disease. It is known that periodontal disease (PD) shares the same risk factors. Moreover, both diseases are characterized by an exaggerated immune response. The aim of the study was to investigate the available evidence of a potential association between PD and the risk of COVID-19 complications and mortality. Materials and Methods: MEDLINE/PubMed, EMBASE, Scopus, and ProQuest were searched. Studies that assess the association between PD and the risk of COVID-19 complications and mortality were eligible for inclusion. Two independent reviewers performed the selection of articles and data extraction. The New Castle Ottawa Scale was used to assess the quality of the selected studies, and the GRADE system was used to evaluate the level of confidence to support the conclusions. Results: Only two studies met the eligibility criteria. One study had a low risk of bias, whereas the other had a high risk of bias. Conclusion: The level of confidence in the available evidence is very low. A close association between periodontitis and the risk of COVID-19 complications and mortality can neither be supported nor refuted.

Keywords: Complications, COVID-19, mortality, periodontitis, SARS-COV-2

Introduction

COVID-19 is an infectious disease caused by the coronavirus SARS-CoV-2. This disease was declared as a pandemic on May 11, 2020 by the World
Health Organization (WHO).[3] It is estimated that more than 4.5 million people were infected during the first 3 months. Meanwhile, this infectious disease continues spreading quickly around the world.[3] The SARS-CoV-2 is transmitted mainly through respiratory droplets during near face-to-face contact. This infection can spread through asymptomatic, pre-symptomatic, or symptomatic carriers.[3]

The COVID-19 manifestations include asymptomatic carriers and sometimes a fulminant disease progression characterized by sepsis and acute respiratory insufficiency. About 5% of all patients with COVID-19 and 20% of hospitalized patients experience severe symptoms requiring intensive care.[4] Between 17% and 35% of the hospitalized patients with COVID-19 are treated more frequently in an intensive care unit (ICU) due to hypoxemic respiratory insufficiency. For patients treated in ICU due to COVID-19, it is estimated that between 29% and 91% require invasive mechanical ventilation.[5-9] Hospitalized patients, besides having respiratory insufficiency, can develop acute renal insufficiency (9%), hepatic dysfunction (19%), septic shock (6%), and coagulation dysfunction or hemorrhage (10–25%).[4] Regarding the mortality, in a cohort of 3988 patients in critical conditions due to SARS-CoV-2 infection, the estimated rates of mortality per 1000 patient-days were 27 (CI of 95%, 26–29) in the hospital and 12 (CI of 95%, 11–12) in the ICU. In the subset of the first 1715 patients, the mortality was 48.8% in ICU and 53.4% in-hospital conditions.[10] COVID-19 is more prevalent in patients who suffer from co-morbidities such as hypertension (present in 48–57% of the patients), diabetes (17–34%), cardiovascular disease (21–28%), chronic pulmonary disease (4–10%), chronic renal disease (3–13%), malignant neoplasm (6–8%), and chronic hepatic disease (<5%).[4]

Periodontitis or periodontal disease (PD) is a chronic inflammatory disease caused by microorganisms and characterized by the progressive destruction of the support apparatus of the tooth that can lead to tooth loss.[11] Recent studies suggest that PD could be associated with COVID-19 complications and mortality.[11,12] PD and COVID-19 present two common characteristics: (1) risk factors such as hypertension, diabetes, cardiovascular disease, and renal and pulmonary disease[6,13-17] and (2) exaggerated immune response characterized by a high release of interferons, interleukins (ILs), tumor necrosis factor (TNF), chemokines, and tissue damage in the more severe presentation of these two diseases.[18-22]

Due to the importance and prevalence of both diseases nowadays, the purpose of this review was to evaluate the available evidence about a potential association between PD and the risk of COVID-19 complications.

**Materials and Methods**

**Registration and protocol**

The protocol for this systematic review was registered in the database of PROSPERO with the code CRD42021244289 (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=244289).

This review was written and conducted according to the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-analyses).[23]

**Focused question**

What is the association between PD and the risk of COVID-19 complications and mortality in adults?

**PECO question: Population, exposure, comparison, outcome**[24]

**Population:** Adults with COVID-19

**Exposure:** Adults with a diagnosis of PD

**Comparison:** Adults without a diagnosis of PD

**Outcome:** Mortality and complications due to COVID-19 such as hospitalization, admission to the ICU, and need for assisted ventilation.

**Search strategies**

The bibliographic search was carried out in several electronic databases such as PubMed, Scopus, EMBASE, and Proquest. The final search date in all the databases was July 23, 2021. There was no time limitation. Hand searches were completed as well. Pre-publication manuscripts were retrieved from preprint servers: bioRxiv, medRxiv, and Google Scholar.

All references were managed using reference management software (RefWorks), and duplicate results were eliminated.

The search strategy considered the following terms: (“periodontitis” OR “periodontal” OR “periodontal disease” OR “periodontal disease risk” OR “periodontal bacteria” OR “periodontal pocket” OR “apical periodontitis” OR “gingivitis” OR “bleeding gum” OR “gum disease” OR “gingival disease” OR “gingival inflammation”) AND (“coronavirus” OR “coronavirus covid-19” OR “novel coronavirus” OR “SARS-CoV” OR “sars cov-2” OR “covid-19” OR “SARS-CoV-2” OR “SARS-CoV” OR “MERS-CoV” OR “2019-nCoV”) [Table 1].

**Inclusion criteria**

Case–control studies and cross-sectional studies were considered.
Exclusion criteria
Interventional studies (RCTs), case series, case reports, pilot studies, editorials, reviews, animal studies, and studies that do not consider co-morbidities were excluded.

Study selection
The initial selection of the articles was carried out independently by two reviewers (D.A.K.E.-E. and O.A.C.-L.) according to the title and abstract. If the abstract was not available, the full text was obtained and evaluated. The full text of all articles was compiled, and the inclusion criteria were verified. Any disagreement was solved by consensus or by the decision of a third author (C.F.C.-R.). The articles that did not meet the selection criteria were excluded from the review, and reasons for exclusion were registered. The description of the selected studies can be seen in Tables 2 and 3.

Evaluation of the study quality
The researchers (D.A.K.E.-E., O.A.C.-L. and C.F.C.-R.) also performed the quality assessment of all the studies; the information was compared, and a consensus was made. To assess the quality of the selected studies, the Quality Access Scale—Newcastle-Ottawa Scale instrument was used. This scale assigns a maximum of 9 points to each study: 4 for exposure selection and assessment, 2 for comparability, and 3 for outcome assessment. If a study receives a score of ≥ 6, it is considered a publication with a low risk of bias [Table 4].

Quality of evidence of the present study—GRADE system
The GRADE system was used to evaluate the certainty of the evidence. It considers five items that may downgrade its certainty: risk of bias, inconsistency, indirect evidence, imprecision, and publication bias. The evidence certainty levels may be scored as follows: high, moderate, low, and very low [Table 5].

Results
The electronic search procedure is presented in Figure 1. A total of 303 studies were initially identified from the electronic databases. After that, 158 duplicate studies were eliminated. Then, titles and abstracts were evaluated, and 143 articles were excluded. No additional studies were found from the hand search of pre-publication manuscripts. Finally, only two articles were included.
| Authors, year of publication, country where the study was carried out, and journal where it was published | Objective | Study design | Sample | Exposure diagnosis: periodontitis | Condition outcome: complications and mortality from COVID-19 | Association measurement | Confusion covariates | Main findings |
|---|---|---|---|---|---|---|---|---|
| 1. Marouf et al. 2021 Qatar Journal of Clinical Periodontology | The objective of this case–control study was to investigate the association of periodontitis with COVID-19 complications. | Case–control | 568 patients diagnosed with COVID-19 who are part of the national electronic medical records of Hamad Medical Corporation (HMC) of the state of Qatar of which 258 presented periodontitis. | The periodontal status was studied from bitewing and panoramic radiographs (OPG) from the patient records. | Condition of complications and mortality from COVID-19 | Association between PD and complications by COVID-19: | Age, sex, smoking, diabetes, co-morbidities, body mass index | Frequency of periodontitis: 45.42% Case group: patients with complications from COVID-19 |

**Case group:** Cases were defined as patients with complications from COVID-19, such as admission to ICU, need for assisted ventilation, or death. The cases consisted of 40 patients of which 33 had periodontitis and 7 did not present periodontitis.

The patients were classified according to periodontitis stages:

1. Death
2. Admission to ICU
3. Need for assisted ventilation

**Control group:** COVID-19 patients discharged without major complications 92.957%

People with at least one of the following criteria:

- Any complication (OR = 3.67, 95% CI 1.46–9.27)
- Mortality (OR = 8.81, 95% CI 1.00–77.7)
- Admission to ICU (OR = 3.54, 95% CI 1.39–9.05)

The study findings showed a strong association between periodontitis and an increased risk of complications from COVID-19.
### Table 2: Continued

| Authors, year of publication, country where the study was carried out, and journal where it was published | Objective | Study design | Sample | Exposure diagnosis: periodontitis | Condition outcome: complications and mortality from COVID-19 | Association measurement | Confusion covariates | Main findings |
|---|---|---|---|---|---|---|---|---|
| 2. Larvin et al. 2020 Reino Unido Frontiers in Medicine | The objective of this study was to quantify the impact of PD on hospital admission and mortality during the COVID-19 pandemic. | Nested case-control | The status of PD was determined by the presence of self-reported oral health indicators such as: bleeding gums, painful gums, and loose teeth. These were used as surrogates for PD, since they have demonstrated their validity in the absence of a clinical diagnosis. | People with at least one of the following criteria: Hospital admission (OR = 0.91, 95% CI 0.12–2.04) 
Association between PD (gum pain or bleeding) and hospitalization of patients with COVID-19: 
Mortality (OR = 1.71, 95% CI 1.05–2.72) | Age, sex, ethnicity, family income, body mass index, smoking history, cancer, hypertension, angina pectoris, heart attack, diabetes, myocardial infarction, | | | |

**Control group:** Controls were defined as COVID-19 patients discharged without major complications.

- Initial periodontitis or periodontally healthy (stages 0-1): bone loss less than the coronal third of the root length (15%) on OPG radiographs, or ≤2 mm on bitewing radiographs.

- Periodontitis (stages 2-4): bone loss greater than the coronal third of the root length (>15%) on OPG, or >2 mm on bitewing radiographs.

**Case group:** Defined as participants with a positive self-reported history of PD.

- People with at least one of the following criteria:
  - Initial periodontitis or periodontally healthy (stages 0-1): bone loss less than the coronal third of the root length (15%) on OPG radiographs, or ≤2 mm on bitewing radiographs.
  - Periodontitis (stages 2-4): bone loss greater than the coronal third of the root length (>15%) on OPG, or >2 mm on bitewing radiographs.

The controls consisted of 528 of which 225 presented periodontitis. Women: 258 Males: 310

13,502 patients tested for COVID-19 (part of UK Biobank database)
| Authors, year of publication, country where the study was carried out, and journal where it was published | Objective | Study design | Sample | Exposure diagnosis: periodontitis | Condition outcome: complications and mortality from COVID-19 | Association measurement | Confusion covariates | Main findings |
|---|---|---|---|---|---|---|---|---|
| **Control group:** Defined as participants with no self-reported history of PD. | Self-reported painful and bleeding gums were associated with mild-to-moderate PD, whereas loose teeth indicated severe PD. | 1. Hospital admission 2. Mortality | Association between PD (tooth loss) and hospitalization of patients with COVID-19: fulminant infarction, peripheral artery disease, heart failure, atrial fibrillation, respiratory disease | Participants with a positive result of COVID-19 1,616 (10.5%) |
| | | | Hospital admission (OR = 0.90, 95% CI 0.16–10.63) Association between PD (tooth loss) and mortality in patients with COVID-19: Mortality (OR = 1.85, 95% CI 0.92–2.72) | | Participants with a negative COVID-19 result 11,637 |

The study findings showed an increased risk of mortality after COVID-19 infection in people with PD, determined by the presence of oral health indicators. While PD may not increase the risk of COVID-19 infection directly, it can increase the risk of death.
## Table 3: Description of outcomes, exposures, and odds ratio results of the relationship between PD and the risk of complications and mortality from COVID-19

| Reference          | Country Design study | Size sample                        | Outcomes                                | Exposures                                | Follow up (a)/(b)/(c)/(d) | Odds ratio results |
|--------------------|----------------------|------------------------------------|-----------------------------------------|------------------------------------------|---------------------------|--------------------|
| Marouf et al. (2021)[1] | Qatar Case-control   | 568 patients diagnosed with COVID-19: 258 women and 310 men | Patient with confirmed COVID-19 diagnosis according to positive PCR test for SARS-CoV-2: Case with complication (n=40; mean age=53.5) Control (n=528; mean age=41.5) | Periodontal condition by radiographic bone loss detection. | 303/7/225/33 | AC: 6.34 (2.79–14.61) |
|                     |                      |                                    | Identify Case Identify Exposed          | Exposed Unexposed with health or initial (stages 0-1): Bone level coronal 1/3 ≤15% (OPGs) or ≤2 mm (bitewing X-ray). | 303/1/225/13 | D: 17.5 (2.27–134.8) 8.81 (1.00–77.7) |
|                     |                      |                                    |                                       | Death (n=14) ICU admission (n=36) Need for assisted ventilation (n=20) | 303/7/225/29 | ICU: 5.57 (2.40–12.9) 3.54 (1.39–9.05) |
|                     |                      |                                    |                                       | Hospital admission (n=4,083) | 303/3/225/17 | NAV: 7.31 (2.21–26.3) 4.57 (1.19–17.4) |
| Larvin et al. (2020)[2] | UK Nested case-control | 13,253 participants of nested case-control data: 6,802 women and 6,451 men | Patient with COVID-19 test result: | Periodontal condition by self-reported oral health indicators. | 9,815/1,338/1,469/225 | PT: 1.07 (0.70–1.63) 1.10 (0.72–1.69) |
|                     |                      |                                    | Case with COVID-19-positive cases (n=1,616; mean age=53.5) Control (n=11,637; mean age=41.5) | Painful and bleeding gums: “mild to moderate PD” | 2,723/665/386/99 | HA: 0.99 (0.13–3.02) 0.91 (0.12–2.94) |
|                     |                      |                                    | Hospital admission (n=4,083) | Loose teeth indicated: “severe PD” | 292/247/37/28 | D: 1.60 (1.03–2.42) 1.71 (1.05–2.72) |
|                     |                      |                                    |                                       | | 9,815/1,338/353/53 | PT: 0.99 (0.73–1.38) 1.15 (0.84–1.59) |
|                     |                      |                                    |                                       | | 2,723/665/101/26 | HA: 0.88 (0.16–10.04) 0.90 (0.16–10.63) |
|                     |                      |                                    |                                       | | 292/247/11/16 | D: 1.34 (0.71–2.76) 1.85 (0.92–2.72) |

(a) control unexposed, (b) case unexposed, (c) control exposed, (d) case exposed, COR = crude odds ratio, AOR = adjusted odds ratio, AC = any complication, CI = confidence interval, PD = periodontal disease, (*) adjusted to principal covariables by age, sex, diabetes, co-morbidity, smoking behavior, D = death, ICU = intensive care unit, NAV = need for assisted ventilation, PT = positive test, HA = hospital admission
One of the two included studies was published in a dental journal, and the other in a medical journal. The sample size varied between 568 patients from Qatar and 13,502 from the UK, with a similar proportion in female and male participants. Regarding the methodological aspects, one was a retrospective case-control and the other a nested case-control. Both studies used national database records. Table 2 provides a summary of the general characteristics of the two included studies.

The characteristics of the study groups were extracted and calculated from the results study tables according to types of exposure of periodontal variables. The cases included definitions such as mortality, need for ventilation assistance, ICU, and hospital admission. All periodontal variables were indirectly classified through bone loss as suggested from radiographs or participants’ self-reports of bleeding and tooth loss. Inferential results on the association of COVID-19 and periodontitis were given in crude and adjusted odds ratios. More information on the studies’ results can be found in Table 3.

The two selected studies had a case-control design; therefore, the critical appraisal verification was carried out concerning eight items for this design (Newcastle-Ottawa Scale). All the items had a score value of one, except the item “comparability of cases and controls based on the design and analysis,” which presented a double score value. Larvin et al.’s studies obtained a score of 5, corresponding to a low-quality evidence publication and a high risk of bias. In contrast, Marouf et al.’s studies obtained a score of 7, which gives the article a high evidence quality value. None of the studies had a score for the item “non-response rate.” Larvin et al.’s study did not receive any score on adequate case definition, nor ascertainment of exposure [Table 4].

The evaluation for quality of evidence using the GRADE system for studies related to the association between PD and the risk of complications and mortality COVID-19 resulted in very low overall certainty [Table 5].

**Discussion**

This systematic review aimed to explore the most recent scientific evidence on the association between PD and the risk of COVID-19 complications and mortality. The current literature on COVID-19 is increasing exponentially. Due to its pandemic nature, it seems important to investigate other possible risk factors. PD has recently been reported as a potential risk factor for higher mortality from COVID-19. The reports indicate that the connection is based on the oral viral load or by cytokines, which have a fundamental role in the immune-inflammatory response to infections, including periodontal pathogens. Although currently these are only hypothetical mechanisms, they present a plausible biological explanation. Previous studies hinted at a probable relation between them. Therefore, the present systematic review aimed to review the available evidence on the association between PD and the risk of COVID-19 complications and mortality.

Only two observational studies met the eligibility criteria of this systematic review, and these were two national multicenter studies from Qatar and the UK. Although these studies do not represent patients from different parts of the world, national records provide epidemiological value on diseases and/or conditions in each country with a lower selection bias. According to the Oxford Center for Evidence-Based Medicine (CEBM), the quality of the evidence concerning the type of study indicates a level 3b for both investigations. The reason for excluding most of the articles was mainly the deficiency or absence of information related to the exposure of periodontitis and results.

Considering the results of the included studies, one of them found a positive association between periodontitis and COVID-19. This study showed statistically significant adjusted results of high probabilities and confidence intervals (CIs) of total complications due to COVID-19, which included death, hospital admission to ICU, assisted ventilation, and clinical parameters of blood levels of white blood cells, D-dimer, and C-reactive protein (CRP) (P < 0.01). The adjusted data controlled probable confounding factors such as smoking, comorbidities, and individual characteristics such as sex or age. Nonetheless, the study is compromised by potential inherent biases due to the retrospective nature of the design and how PD was diagnosed. The methodological evaluation of PD measurement used the concept of radiographic bone loss percentage and its grouping according to periodontal stages. The absence of clinical parameters such as probing depth, clinical attachment level (CAL), bleeding on probing (BOP), plaque index (PI), and tooth loss limits the diagnostic interpretation of PD.

Further, they evaluated biomarkers such as D-dimer, CRP, HbA1c, vitamin D, white blood cells, and lymphocytes. This information is of interest to indirectly evaluate PD and the link between PD and COVID-19 complications as they present immunological, microbiological, and biochemical expressions.
However, the coexistence of both diseases linked to the production of inflammatory biomarkers is a source of potential bias for data interpretation.

The negative association of variables from the study carried out in the UK is likely a consequence of its solid sample size of 13,253 participants.[12] The sample is based on a cohort of national data records considered representative of the country. This is an important methodological feature when selecting controls. The statistics were not conclusive concerning PD and COVID-19 as the result of the applied multivariate regression was less than 1, except the probability of mortality in cases of bleeding or painful gums \([\text{OR} = 1.71; 95\% \ CI \ (1.05–2.72)]\). As in the study mentioned before, confounding factors and socioeconomic variables and ethnicity were controlled.

The study authors reported underestimating cases as a relevant weakness; this could be explained by the short period the patients stayed in the hospital or the number of deaths. In that sense, the PD cases could have been underestimated in the selection. Perhaps, the most relevant weakness of the study is related to the diagnosis of PD, which was self-reported by the participants regarding pain and/or bleeding of the gums and tooth loss. The reliability of the data is biased in that sense as no clinical/radiological evaluation was performed. Finally, the information did not filter previous periodontal treatments, which could have underestimated the identification of PD.

The risk of bias found using the Newcastle-Ottawa scale showed that even though the study by Marouf et al. had weakness in the way PD had been determined, the case definition was extracted from valid records.[28,29] In contrast, the study by Larvin et al. used self-report to determine the cases, which does not represent a reliable source for an adequate clinical case definition, nor is it a reliable method of ascertainment of cases and controls.[12,30] As the non-response rate had not been specified, none of the studies received any score in this item.

Regarding the possible theoretical explanation between PD and the risk of COVID-19 complications and mortality, there is evidence that supports this hypothesis, such as the association between periodontitis and other systemic diseases such as diabetes, cardiovascular disease, adverse pregnancy outcomes, rheumatoid arthritis, chronic obstructive pulmonary disease, inflammatory bowel disease, and chronic kidney disease.[31-34] COVID-19 virus infects human cells by binding the viral spike protein (S) with angiotensin-converting enzyme 2 (ACE 2), a cellular receptor highly expressed in type II pneumocytes, macrophages, endothelial cells, and other lung cells.[35-37] This binding triggers the production of inflammatory cytokines capable of inducing intravascular coagulopathy and thrombotic complications in pulmonary blood vessels.[35,36,38,39] Although it mainly affects the lungs, the SARS-CoV-2 virus also affects the cardiovascular
system. The vasculature is affected in COVID-19, both directly by the SARS-CoV-2 virus and indirectly due to a storm of systemic inflammatory cytokines. This includes the role of vascular endothelium in the recruitment of inflammatory leukocytes where they contribute to the tissue damage and the release of cytokines, which are key drivers of acute respiratory distress syndrome, in disseminated intravascular coagulation and cardiovascular complications in COVID-19.[40]

In patients who develop the most severe forms of COVID-19, there is a high incidence of macro- and microvascular thrombosis, prolonged hospitalization, and risk of death. This is attributed to a “cytokine storm,” with elevated serum levels of inflammatory cytokines (IL-6, IL-1, IFN-γ) and endothelial activation markers such as von Willebrand factor, coagulation factor 8, and P-soluble selectin, resulting in endothelialitis and microvascular thrombosis.[41,43] Del Valle et al.[44] identified high serum levels of IL-6 and TNF-α when the progression of the disease required the patient to be hospitalized. Moreover, it has been suggested that age-related drop in host’s immunity (immunosenescence) combined with a low-grade chronic systemic inflammation predisposes patients to further complications when infected with SARS-CoV-2.[45,46] In addition to severe injury to local tissues, there are systemic consequences such as direct lung injury, acute respiratory distress syndrome, multiple organ failure, and unfavorable prognosis.[47-49] Likewise, it has been reported that in severe cases of COVID-19, the leading cause of death is respiratory failure associated with excessive inflammation.[50]

It has been described that the aspiration of periodontal pathogens could increase the severity of the infection of the lungs by SARS-CoV-2.[51] Besides, it has been reported that aspiration of saliva with a high viral load can transport the virus to the lower respiratory tract, increasing the risk of developing more severe forms of the disease.[52]
On the contrary, it is mentioned that inflamed periodontal tissues would act as a reservoir of pro-inflammatory cytokines (TNF-α, IL-1 α, IL-1 β and IL-6) that could be systemically disseminated through the blood circulation, exacerbating the pre-existing systemic inflammation.[53-55] Furthermore, the infection of alveolar epithelial cells by SARS-COV-2 generates an active acute inflammatory response to macrophages, B and T lymphocytes for the release of pro-inflammatory cytokines. These inflammatory factors induce large amounts of inflammatory exudate and red blood cells to enter the pulmonary alveoli, resulting in dyspnea, respiratory failure, and death.[56-58] This would explain the findings of a significant presence of microthrombi and vascular injury in post-mortem reports of patients with COVID-19.[59]

Another association mechanism between periodontitis and COVID-19 is the effect of prolonged exposure to Porphyromonas gingivalis lipopolysaccharides and other periodontal pathogens. These bacterial products produce accelerated senescence of different types of cells, including the pulmonary epithelial cells. This effect facilitates the entry and promotes the viral replication of SARS-CoV-2.[60] In contrast, Shivshankar et al.[61] showed that senescent cells promote bacterial adhesion to lung cells, eventually resulting in increased susceptibility to bacterial-induced pneumonia in older adults.

Additionally, PD has been associated with various factors and co-morbidities such as diabetes, obesity, advanced age, and high blood pressure; likewise, these factors have also been associated with the progression or severity of COVID-19. Since inflammatory factors seem to play an important role affecting systemically both PD and COVID-19, it is possible to think that periodontal status can be considered a risk indicator for complications of COVID-19.[62,63] However, in view of the statement that PD and COVID-19 present two common characteristics: (1) risk factors such as hypertension, diabetes, cardiovascular disease, and renal and pulmonary disease[4,13-17] and (2) exaggerated immune response characterized by a high release of interferons, ILs, TNF, chemokines, and tissue damage in the more severe presentation of these two diseases,[18-22] one wonders how a potential association between PD and the risk of COVID-19 complications could/should be interpreted.

The available evidence does not conclusively support an association between periodontitis and the risk of complications and mortality from COVID-19. However, the findings obtained by the studies included in this review suggest that this association may be feasible. More research is needed to minimize methodological and clinical heterogeneity between studies, particularly regarding the characteristics of the samples and the definition of the most relevant results. Additionally, various biological mechanisms could be considered as factors supporting the association between both diseases.

In addition, both periodontitis and the risk of complications such as hospitalization, ICU admission, the need for assisted ventilation, and mortality from COVID-19 are public health concerns in this pandemic. These findings could also suggest the need for additional actions to implement prevention measures and promote oral health in people who suffer from periodontitis and have risk factors such as hypertension, diabetes, cardiovascular disease, kidney disease, and lung disease.

**CONCLUSION**

The level of confidence in the available evidence is very low. A close association between periodontitis and the risk of COVID-19 complications and mortality can neither be supported nor refuted.

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The authors declare that this review was carried out with our own resources.

**CONFLICTS OF INTEREST**

None to declare.

**AUTHORS CONTRIBUTIONS**

All authors equally contributed to the paper.

**ETHICAL POLICY AND INSTITUTIONAL REVIEW BOARD STATEMENT**

Not applicable.

**PATIENT DECLARATION OF CONSENT**

Not applicable.

**DATA AVAILABILITY STATEMENT**

Not applicable.

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