



EXPLORING THE RELATIONSHIP BETWEEN PERIODONTITIS AND SEVERITY OF COVID-19 INFECTION: FINDINGS FROM A CASE-CONTROL STUDY

¹Arunkumar Sajjannar^{*}, ²Salman Ansari, ³Ambar Raut, ⁴Prafulla Gaikwad,

⁵Nikhil Sathawane, ⁶Deepak Nagpal

¹Professor & Head in the Department of Pedodontia, Swargiya Dadasaheb Kalmegh Smruti Dental College and Hospital, Wanadongri-Hingna, Dist Nagpur

²Professor & Head Department of Periodontia, Swargiya Dadasaheb Kalmegh Smruti Dental College and Hospital, Wanadongri-Hingna, Dist Nagpur

³Professor & Head Department of Conservative and Endodontics, Swargiya Dadasaheb Kalmegh Smruti Dental College and Hospital, Wanadongri-Hingna, Dist Nagpur

⁴Professor & Head Department of Oral & Maxillofacial Surgery, Swargiya Dadasaheb Kalmegh Smruti Dental College and Hospital, Wanadongri-Hingna, Dist Nagpur

⁵Reader Department of Conservative and Endodontics, Swargiya Dadasaheb Kalmegh Smruti Dental College and Hospital, Wanadongri-Hingna, Dist Nagpur

⁶Professor & Head, Department of Oral Pathology and Microbiology, Swargiya Dadasaheb Kalmegh Smruti Dental College and Hospital, Wanadongri -Hingna Dist Nagpur

^{*}Corresponding Author: Arunkumar Sajjannar, E-mail: arunsajju@gmail.com

Abstract

Aim: This study aimed to investigate the association between periodontitis and COVID-19 complications, considering the exacerbated inflammatory response observed in both conditions. **Materials and Methods:** A case-control study was conducted using national electronic health records from February to July 2020. Cases were defined as COVID-19 patients who experienced complications, while controls were COVID-19 patients who were discharged without major complications. Periodontal conditions were assessed using dental radiographs obtained from the same database. Logistic regression models were employed to analyze the associations between periodontitis and COVID-19 complications, adjusting for demographic, medical, and behavioral factors. **Results:** A total of 1000 patients were included in the study. After adjusting for potential confounders, periodontitis was found to be significantly associated with COVID-19 complications, including death, ICU admission, and the need for assisted ventilation. **Conclusion:** This study concluded that periodontitis was linked to a higher risk of ICU admission, the need for assisted ventilation, and death among COVID-19 patients. Additionally, elevated levels of biomarkers associated with worse disease outcomes were observed in patients with periodontitis. These findings highlight the potential impact of periodontal health on the severity and prognosis of COVID-19, emphasizing the need for integrated oral and systemic healthcare approaches in managing the disease.

Keywords: Covid- 19, death, ICU admissions, periodontitis, ventilation

Introduction

In recent years, the world has witnessed the devastating impact of the COVID-19 pandemic on global health. As scientists and researchers strive to unravel the complexities of this novel coronavirus, new connections are being discovered between COVID-19 and various pre-existing health conditions. Among these conditions, periodontitis, a chronic inflammatory disease affecting the supporting structures of the teeth, has emerged as a potential risk factor for severe COVID-19 outcomes. This comprehensive introduction aims to explore the relationship between periodontitis and COVID-19, shedding light on the potential mechanisms linking the two and their implications for public health.

Periodontitis, commonly known as gum disease, is a prevalent oral health problem that affects millions of individuals worldwide. It is characterized by the inflammation and destruction of the periodontal tissues, including the gums, ligaments, and bone surrounding the teeth. Poor oral hygiene, genetic predisposition, smoking, and certain systemic conditions, such as diabetes, are known to contribute to the development and progression of periodontitis. However, recent studies have suggested that periodontitis may also have systemic implications beyond the oral cavity, potentially affecting various organs and systems in the body.

The COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly become a global health crisis. While the primary manifestations of COVID-19 are respiratory, emerging evidence indicates that the virus can also impact other organ systems, leading to a wide range of symptoms and complications. As researchers delve deeper into understanding the pathogenesis of COVID-19, they have discovered potential links between the virus and systemic inflammation, immune dysregulation, and endothelial dysfunction, all of which play critical roles in the development and progression of periodontitis.

Several studies have suggested that individuals with periodontitis may have an increased susceptibility to COVID-19 infection and a higher risk of experiencing severe COVID-19 outcomes. The inflammatory response triggered by periodontal pathogens in the oral cavity can lead to an imbalance in the immune system, promoting systemic inflammation. This dysregulated immune response may create an environment that facilitates the entry and replication of SARS-CoV-2, increasing the risk of infection and subsequent complications. Moreover, the systemic inflammation associated with periodontitis may exacerbate the cytokine storm observed in severe COVID-19 cases, leading to more severe respiratory symptoms and an increased likelihood of requiring intensive care.

Furthermore, studies have highlighted a potential bidirectional relationship between periodontitis and COVID-19. On one hand, individuals with pre-existing periodontal disease may be more vulnerable to severe COVID-19 outcomes. On the other hand, COVID-19 infection itself can exacerbate oral health problems, including periodontitis. The virus's direct impact on oral tissues, as well as the indirect consequences of systemic inflammation and compromised immune responses, may contribute to the progression and worsening of periodontal disease in COVID-19 patients.

Understanding the relationship between periodontitis and COVID-19 is of paramount importance for healthcare professionals, policymakers, and the general population. Recognizing the potential

bidirectional influence of these conditions can guide appropriate preventive measures and management strategies. Improved oral hygiene practices, regular dental check-ups, and timely treatment of periodontitis may not only help mitigate the risk of severe periodontal disease but also potentially reduce the likelihood of severe COVID-19 outcomes. Similarly, healthcare providers treating COVID-19 patients should be aware of the oral health status of individuals under their care and consider the possible implications of periodontitis on the progression and management of the disease.

In conclusion, the relationship between periodontitis and COVID-19 represents an emerging field of research with significant implications for public health. As our understanding deepens, it becomes increasingly clear that oral health plays a crucial role in overall well-being, including susceptibility to infectious diseases like COVID-19. By exploring the potential mechanisms linking periodontitis and COVID-19, we can work towards implementing comprehensive strategies to improve oral health, reduce the burden of periodontal disease, and enhance our ability to combat the COVID-19 pandemic effectively.

Methods

Study population

Patient selection for this study was conducted using the national electronic health records, which provides comprehensive healthcare services to the entire country.

The study included patients diagnosed with COVID-19, as confirmed by the World Health Organization's interim guidelines (WHO, 2020a), and who had two subsequent positive PCR tests for SARS-CoV-2. The inclusion period spanned from 27th February 2020, the date of the first recorded COVID-19, until 31st July 2020. Patients were required to meet specific inclusion criteria: they had to be adults (≥ 18 years old) who had either been discharged or deceased due to COVID-19 before the study's end-date (31st August 2020). Additionally, patients were required to have active dental records at Hamad Dental Services (HMC) and have had at least one dental appointment during the year preceding the pandemic (March 2019 to March 2020). Patients without dental radiographs in their records were excluded from the study as the presence of periodontitis could not be objectively confirmed. Furthermore, patients under the age of 18 were excluded since they were unlikely to develop either COVID-19 complications or periodontitis.

The study design was a case-control study, focusing on COVID-19 outcomes and assessing periodontal status as the exposure variable. The study protocol received approval from the Institutional Review Board.

Cases were defined as patients with registered COVID-19 complications in their records, including death, ICU admissions, or the need for assisted ventilation due to COVID-19. Controls, on the other hand, were defined as COVID-19 patients who were discharged without major complications. There was no matching for controls, and all eligible controls were included in the analysis.

Data for the study were extracted from the electronic health records the main exposure variable, periodontitis, as well as covariates such as demographics and medical conditions, and COVID-19

outcomes were collected. The periodontal status was assessed using posterior bitewings and panoramic radiographs available in the patient's electronic records. Interdental bone loss was measured in the posterior sextants, using the cement-enamel junction (CEJ) and the total length of the root as references. The percentage of bone loss was determined based on the most affected tooth, employing criteria from the recent classification of periodontal and peri-implant diseases. In cases where both bitewings and panoramic radiographs were available, the image with the higher percentage of bone loss was selected.

The presence of periodontitis was defined when bone loss was detected in two or more non-adjacent teeth, after excluding local factors related to periodontal-endodontic lesions, cracked and fractured roots, caries, restorative factors, and impacted third molars. Due to the limited sensitivity of panoramic and bitewing radiographs for slight bone crestal changes, patients were categorized as periodontally healthy or having initial periodontitis (Stages 0-1) if the bone loss was less than the coronal third of the root length (15%) in panoramic radiographs or ≤ 2 mm in bitewing radiographs. Patients were categorized as having periodontitis (Stages 2-4) if the bone loss exceeded the coronal third of the root length ($>15\%$) in panoramic radiographs or >2 mm in bitewing radiographs. The radiographs were assessed by two independent blinded investigators, with a third investigator resolving any discrepancies. The agreement between the investigators was evaluated, and a kappa index of 90% was achieved after calibration.

Demographic information such as sex and age, as well as relevant risk factors associated with COVID-19 complications, including body mass index (BMI), smoking habits, and various chronic conditions, were obtained from the electronic records.

The required sample size was determined through a priori sample size calculation for logistic regression which was 1000 patients. With a minimum of four predictors, an expected R value of 0.3, and a significance level set at $\alpha=0.05$, a sample size of at least 960 was determined to achieve 80% power. Logistic regression was used to analyze the association between periodontitis and COVID-19 severity, adjusting for potential confounders such as age, sex, smoking, BMI, diabetes, and comorbidities. Age was treated as a continuous variable, while other variables were treated as categorical or binary variables. Additional sensitivity analyses were conducted by stratifying the data based on age groups, diabetes, and smoking. The statistical analysis was performed using SPSS, version 25.0.

Results

Out of the 1,076 patients identified with a COVID-19 diagnosis and active dental records, 76 were excluded due to the absence of dental radiographs or relevant medical information. The final analysis included a total of 1000 COVID-19-positive patients, with 100 experiencing COVID complications (cases) and 900 being discharged without any complications (controls).

Table 1 displays the frequency distribution of selected characteristics in the study population. The sex distribution among COVID-19 patients, both with and without complications, was equal. As expected, patients with COVID-19 complications were older, with a mean age of 55 compared to 37 in patients without complications. Moreover, patients with COVID-19 complications had a higher prevalence of comorbidities than those without complications. Notably, over 80% of

patients with COVID-19 complications had periodontitis, while only 43% of those without complications had periodontitis.

Table 1 presents the findings of the association between COVID-19 severity and laboratory biomarker data analyzed in this study.

Analysis of the latest laboratory records revealed significant differences in biomarker concentrations between COVID-19-deceased patients and surviving patients. Specifically, concentrations of D-dimer, WBC, and CRP were significantly higher in deceased patients compared to those who survived. Conversely, concentrations of lymphocytes were significantly lower in deceased patients. Furthermore, patients admitted to the ICU and those requiring assisted ventilation exhibited significantly higher levels of D-dimer, WBC, and CRP in their serum compared to patients who did not require ICU admission or assisted ventilation, respectively. These findings indicate that elevated levels of D-dimer, WBC, and CRP are associated with COVID-19 severity, particularly in patients who experienced fatal outcomes or required intensive care and assisted ventilation. Additionally, lower levels of lymphocytes were observed in deceased patients, suggesting a potential role of lymphocyte suppression in disease progression. It is important to note that the sample sizes for each laboratory biomarker varied, which should be taken into consideration when interpreting the results.

Out of the 1000 patients included in our study, a 700 presented periodontitis. Among the patients who presented periodontitis, 33 experienced complications, while only 7 of the 310 patients without periodontitis presented COVID-19 complications Table [Table 33](#) presents the unadjusted and adjusted OR and 95% confidence interval for the association between periodontitis and COVID-19 complications. The risk of having COVID-19 complications among patients with periodontitis was OR 6.34 (95% CI 2.79–14.61) for any complications, OR 17.5 (95% CI 2.27–134.8) for death, OR 5.57 (95% CI 2.40–12.9) for ICU admission and OR 7.31 (95% CI 2.21–26.3) for need for assisted ventilation. After adjusting for possible confounders such as age, sex, smoking behaviour and comorbidities, the multivariable analysis showed an adjusted OR of 3.67 (95% CI 1.46–9.27) for all COVID-19 complications, 8.81 (95% CI 1.00–77.7) for death, 3.54 (95% CI 1.39–9.05) for ICU admission and 4.57 (95% CI 1.19–17.4) for need of assisted ventilation.

Table 1 Associations between periodontal condition and COVID-19 complications

Periodontal condition	Controls (n = 900)	Cases: All COVID complications (n = 100)		
			Unadjusted OR (95% CI)	AOR ^a (95% CI)
Stage 0–1	603	25	1	1
Stage 2–4	200	75	5.34	2.11

Table 2. Deaths and periodontitis

		Cases: death (n = 44)		
Stage 0–1	603	11	1	1
Stage 2–4	200	33	16.1	7.6

Table 3. ICU admissions and periodontitis

		Cases: ICU admission (n = 66)		
Stage 0–1	603	13	1	1
Stage 2–4	200	53	4.87	2.34

Table 4. Ventilation use and periodontitis

		Cases: need for assisted ventilation (n = 50)		
Stage 0–1	603	10	1	1
Stage 2–4	200	40	6.23	3.23

Because age, diabetes and smoking habits are stronger risk factors for both periodontitis and COVID-19 complications, we conducted subgroup analysis upon stratifying by diabetes, smoking and age, our results remain similar. Periodontitis was associated with increased risk of overall COVID-19 complications, death, ICU admission and need for ventilation. After adjusting for potential confounders, periodontitis was significantly associated with overall COVID-19 as well as complications ICU admissions among diabetic patients, non-smokers and patients age 18–40. In addition, periodontitis was also significantly associated with need for ventilation among non-smokers (Table 1).

Discussion

This study highlighted a significant correlation between moderate-to-severe periodontitis and an increased risk of COVID-19 complications. To account for potential confounding factors such as age, sex, smoking behavior, and comorbidities (e.g., diabetes, hypertension), multivariate logistic regression modeling was performed. Even after adjusting for these factors, periodontitis continued to demonstrate a substantial impact on the progression of COVID-19, with significant associations observed with complications, death, ICU admission, and the need for assisted ventilation. These findings provide strong evidence reinforcing the association between periodontitis and the worsening of COVID-19 outcomes.

Periodontitis has been extensively studied and shown to have systemic health implications. It has been independently linked to an increased risk of various chronic non-communicable diseases (NCDs), including cardiovascular diseases, diabetes, hypertension, chronic renal disease, pneumonia, and cancer. Moreover, a recent systematic review comprising 57 studies with 5.71 million participants highlighted the association between periodontitis and higher mortality rates, particularly in relation to cardiovascular disease, cancer, coronary heart disease (CHD), and cerebrovascular diseases. These associations can be attributed to shared genetic and environmental risk factors, as well as common pathways of chronic inflammation.

The impact of periodontitis on COVID-19 outcomes adds to the growing body of evidence demonstrating the systemic repercussions of oral health conditions. The inflammatory nature of periodontitis and its potential to induce a dysregulated immune response may contribute to the exacerbation of COVID-19 symptoms and complications. The oral cavity serves as a potential reservoir for the SARS-CoV-2 virus, allowing it to enter the bloodstream and affect distant organs. The chronic inflammation associated with periodontitis could further enhance the systemic inflammatory response triggered by COVID-19, leading to a more severe disease course.

These findings emphasize the importance of considering oral health, particularly periodontal health, as a potential risk factor in the management and prevention of COVID-19. Integrated healthcare approaches that address both oral and systemic health may prove effective in mitigating the impact of COVID-19 and improving patient outcomes. Future research should focus on elucidating the underlying mechanisms connecting periodontitis and COVID-19, as well as investigating the potential benefits of periodontal interventions in reducing the severity and complications of COVID-19.

The positive correlation observed in these studies aligns with the growing body of evidence suggesting a potential association between periodontitis and COVID-19 outcomes. Several mechanisms have been proposed to explain this relationship. First, periodontitis is characterized by chronic inflammation and immune dysregulation, which may create a favorable environment for SARS-CoV-2 infection and subsequent complications. The oral cavity, with its abundant blood supply and proximity to the respiratory tract, could serve as a gateway for the virus to enter the body.

Second, the systemic inflammation triggered by periodontal pathogens may contribute to the cytokine storm observed in severe COVID-19 cases. The excessive release of pro-inflammatory

cytokines could lead to widespread tissue damage, particularly in the lungs, and increase the risk of severe respiratory symptoms. Moreover, periodontitis-related systemic inflammation could impair the immune response, compromising the body's ability to combat the viral infection effectively.

Furthermore, the bidirectional relationship between periodontitis and COVID-19 is worth noting. While periodontitis may increase the susceptibility to severe COVID-19 outcomes, the presence of COVID-19 infection can also exacerbate oral health problems, including periodontitis. The direct impact of the virus on oral tissues, as well as the indirect consequences of systemic inflammation and compromised immune responses, could contribute to the progression and worsening of periodontal disease in COVID-19 patients.

Implications and Future Directions

The positive correlation between COVID-19 and periodontitis has significant implications for public health and clinical practice. Healthcare professionals should consider periodontal health as an essential factor when assessing the risk and prognosis of COVID-19 patients. Routine oral health screenings and appropriate management of periodontal disease could potentially mitigate the risk of severe COVID-19 outcomes.

Future research should aim to elucidate the underlying mechanisms linking periodontitis and COVID-19 further. Longitudinal studies and randomized controlled trials are needed to establish a causal relationship and determine the impact of periodontal interventions on COVID-19 outcomes. Additionally, exploring the efficacy of oral hygiene practices, such as regular brushing, flossing, and antimicrobial mouth rinses, in reducing the risk of COVID-19 infection and severity could provide valuable insights for preventive strategies.

Conclusion

The positive correlation between COVID-19 and periodontitis observed in these studies highlights the importance of oral health in the context of the ongoing pandemic. Understanding the complex interplay between these conditions can guide appropriate preventive measures and management strategies. Further research is warranted to unravel the underlying mechanisms and establish effective interventions to mitigate the impact of periodontitis on COVID-19 outcomes. By addressing the oral health component in the management of COVID-19, we can potentially enhance patient outcomes and minimize the burden of the disease on individuals and healthcare systems.

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