



ORIGINAL ARTICLE

Association between periodontitis and COVID-19 severity in a tertiary hospital: A retrospective cohort study



Nora Alnomay^{a,b}, Layan Alolayan^c, Raghad Aljohani^c, Razan Almashouf^c, Gharam Alharbi^d

^a Dental Center, Central Region, King Abdulaziz Medical City, Saudi Arabia

^b College Of Dentistry, King Saud Bin Abdulaziz University for Health Sciences/King Abdullah International Medical Research Center, Ministry Of National Guard, Riyadh, Saudi Arabia

^c College Of Dentistry, King Saud Bin Abdulaziz University For Health Sciences/King Abdullah International Medical Research Center, Ministry Of National Guard, Riyadh, Saudi Arabia

^d College Of Dentistry, Qassim University, Qassim, Saudi Arabia

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KEYWORDS

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Abstract *Introduction:* Periodontitis is a chronic inflammatory disease caused by biofilm accumulation resulting in loss of periodontal attachment which could be linked to systemic implications. Coronavirus disease of 2019 (COVID-19) is a disease caused by SARS-CoV-2 that triggers damage to the lungs and other organs. COVID-19 and periodontitis share similar risk factors such as smoking, obesity, old age, and diabetes mellitus. Studies noted that periodontitis along with some systemic diseases has increased mortality. Thus, this study aims to examine the association of periodontitis with COVID-19 outcomes.

Methods: This observational study included periodontitis group and non-periodontitis group for COVID-19 outcome assessment. Inclusion criteria were applied to select adults (≥ 18 years old) who showed at least one dental visit, and were isolated or admitted due to a COVID-19 complication (i.e. in-ward, ICU, or death). Exclusion criteria were patients with no active dental records. The periodontal status was examined from posterior bitewings and panoramic radiographs. The primary outcome assessed was COVID-19 complications versus no admission.

Results and discussion: This study was the first of its kind as a retrospective cohort study to assess the association between periodontitis and COVID-19 severity in Riyadh, Saudi Arabia.

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Our findings revealed that periodontitis is statistically associated with COVID-19 severity. Periodontitis patients were three times more likely to have COVID-19 complications ($p = 0.025$). Diabetes ($p = 0.004$) and hypertension ($p = 0.016$) patients were 3.5 times more likely to have COVID-19 complications.

Conclusion: Understanding the potential association between periodontitis and COVID-19 through systemic inflammation might be a pathway to achieve high quality medical care.

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1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a member of the Coronaviridae family that spread rapidly through Wuhan, China, in the late months of 2019, and then worldwide (Pal et al., 2020). On March 11, 2020, the World Health Organization (WHO) declared it a global pandemic and referred to it as coronavirus disease of 2019 (COVID-19) (WHO, 2020). Though most COVID-19 patients exhibit mild to moderate symptoms ranging from fever, fatigue, and myalgia to dry cough, sore throat, and diarrhea, some patients suffer from severe complications (Guo et al., 2020). Blood clots, pneumonia, sepsis, septic shock, and acute respiratory distress syndrome (ARDS) requiring hospitalization and oxygen support are considered the main complications presented in 20 % of patients (Guo et al., 2020; Huang et al., 2020). Those who present with COVID-19 complications have been reported to have higher levels of inflammatory markers, such as IL-6, IFN γ , and IL-1 β , as well as bacteria and neutrophil-to-lymphocyte counts (Sampson et al., 2020; Tay et al., 2020).

Periodontium refers to the composition of the gingiva, root cementum, alveolar bone, and periodontal fiber apparatus that maintains teeth and aids in mastication (Li et al., 2020). Periodontal health was defined by the 2018 World Workshop of the European Federation of Periodontology (EFP) and the American Academy of Periodontology (AAP) as an absence of clinically detected inflammation (Mariotti and Hefti, 2015). Periodontitis is a chronic multifactorial inflammatory disease that results in loss of periodontal attachment and is associated with long-term biofilm accumulation (Könönen et al., 2019). Factors that increase the risk of periodontitis can be classified into modifiable and non-modifiable factors. Modifiable risk factors include poor oral hygiene, smoking, obesity, and diabetes mellitus, whereas the main non-modifiable factor is age (Khan et al., 2018; Nazir, 2021). Periodontitis disrupts the mutual dynamic of the oral microbiota, promoting the release of proinflammatory cytokines (Hajishengallis, 2015; Sukumar and Tadepalli, 2021). This disruption further affects the bacteria present in dental biofilm, resulting in increased cytokine release in saliva (Hajishengallis, 2015).

The integration of oral health and systemic health is well established in the literature, and it has been linked to the majority of chronic non-communicable illnesses, including diabetes mellitus, hypertension, and cardiovascular disease (Kim and Amar, 2006; Nazir, 2021). Evidence of the influence of oral disease on the occurrence and/or progression of various systemic diseases over the years has piqued the interest of researchers from different fields. Studies have noted that the

presence of periodontitis along with other systemic diseases increases the mortality rate (Kim and Amar, 2006). Similarly, the presence of systemic diseases has been linked to the severity of symptoms in patients with COVID-19 (Liu et al., 2020). A recent study done in the State of Qatar concluded that COVID-19 patients with periodontitis are more likely to be hospitalized, ventilated, or die (Marouf et al., 2021). Thus, it can be hypothesized that the status of COVID-19 patients is aggravated by periodontitis. Therefore, understanding the association between oral diseases and other diseases through systemic inflammation is a core concept in identifying the possible influence of periodontitis on COVID-19 complications. Despite extensive research on COVID-19 complications, the association between periodontitis and COVID-19 complications is still inadequately reported. The main aim of the present study was to investigate the association between periodontitis and COVID-19 severity in the central region of Saudi Arabia.

2. Methods

2.1. Design

This study was a retrospective cohort study including patients who were diagnosed with periodontitis and COVID-19 between January 2020 and July 2021. All patients were selected from the Best-Care electronic system used at King Abdulaziz Medical City (KAMC), Riyadh, Saudi Arabia, after obtaining approval # IRBC/1269/21 from the Institutional Review Board (IRB) of King Abdullah International Medical Research Center (KAIMRC).

2.2. Patients and data collection

Inclusion criteria were applied to select adult patients (≥ 18 years old) who had at least one dental visit from January 1, 2020, to July 30, 2021, and were diagnosed with COVID-19 and discharged or admitted for reporting a COVID-19 complication (i.e., in-ward, ICU admission, or death). Exclusion criteria were no dental radiographs or periodontitis caused by local factors related to periodontal-endodontic lesions, cracked and fractured roots, caries, restorative factors, or impacted third molars. A total of 1705 patients who had a COVID-19 diagnosis had active dental records, but 1517 were excluded due to a lack of dental radiographs. Thus, a total of 188 COVID-19 patients were included in the study. Patient data included demographic features, smoking status, laboratory results, and the presence of comorbidities (e.g., diabetes, hypertension, respiratory disorders, endocrine disorders, cardiovascular disorders, obesity, cancer, kidney dialysis, or

organ transplant). The periodontal status was examined on posterior bitewings and panoramic radiographs taken with Planmeca Romexis 6.0.1.812® software. Interdental bone loss was measured in the posterior sextants using cemento-enamel junction and the total length of the root as a reference. The percentage of bone loss was obtained from the most affected tooth using the criteria from the recent classification of periodontal and *peri*-implant diseases (Jepsen et al., 2018). Each radiograph was assessed by two blinded investigators. The primary outcome was COVID-19 complications (i.e., in-ward, ICU admission, or death) vs not admitted (home/facility isolation).

2.3. Statistical analysis

Logistic regression analysis was conducted to identify the predictors of complication development. The dependent variable was complications (yes/no). The independent variables were included based on clinical judgment (periodontitis, diabetes mellitus, hypertension, obesity, and being a smoker). Results are reported as odds ratios (ORs) with corresponding 95 % confidence intervals (CIs) and p-values. A p-value < 0.05 was considered significant.

3. Results

3.1. Characteristics of COVID-19 patients

Among the 188 COVID-19 patients included in the study, 99 had periodontitis (Table 1). Table 2 outlines specific characteristics of the study population and frequency distributions for the two groups of COVID-19 patients, those with periodontitis and those without. The two groups were almost equally distributed in terms of gender. However, the prevalence of diabetes and hypertension was higher in the periodontitis group than in the non-periodontitis group. Moreover, the periodontitis group was older (>45 years old) and had more comor-

Table 1 Overall characteristics of covid-19 patients.

Periodontitis	
Yes	99
No	89
Gender	
Male	43 %
Female	56.9 %
Smoking	
Yes	8.5 %
No	91.4 %
Diabetes	
Yes	23.5 %
No	76.4 %
Hypertension	
Yes	13.8 %
No	86 %
Obesity	
Yes	36.7 %
No	63.3 %
Comorbidities	
Yes	64.8 %
No	34.5 %

Table 2 Selected characteristics of covid-19 patients.

	Periodontitis group	Non-periodontitis group
Gender		
Male	47 (25 %)	34 (18.09 %)
Female	52 (27.66 %)	55 (29.26 %)
Mean age, years (SD)	49.38 (13.63)	33.54 (9.76)
Smoking		
Yes	11 (5.85 %)	5 (2.66 %)
No	88 (47.81 %)	84 (44.68 %)
Diabetes		
Yes	36 (19.25 %)	8 (4.28 %)
No	62 (33.16 %)	81 (43.31 %)
Hypertension		
Yes	20 (10.64 %)	6 (3.19 %)
No	79 (42.02 %)	83 (44.15 %)
Obesity		
Yes	48 (25.53 %)	21 (11.17 %)
No	51 (27.13 %)	68 (36.17 %)
Comorbidities		
Yes	77 (40.96 %)	45 (23.94 %)
No	21 (11.17 %)	44 (23.40 %)

bidities. The periodontitis group also had more smokers, but this measure is not reliable due to the lack of data in the dental records.

3.2. COVID-19 complications

Table 3 outlines the complications of COVID-19 that can impact the two groups in three different ways: ward admission, ICU admission, and death. According to our results, 12.23 % of the periodontitis patients were admitted to the ward to receive assisted ventilation, whereas only 3.72 % of non-periodontitis needed to be admitted. Furthermore, 3.19 % were admitted to the ICU and 1.6 % who died were in the periodontitis group.

3.3. Laboratory tests in COVID-19 patients

Table 4 shows the correlation between the laboratory biomarkers in both groups and the incidence of complications associated with COVID-19. Laboratory records on WBC, HbA1c, C-reactive protein (CRP), and Erythrocyte sedimentation rate (ESR) were recorded for the 188 patients. We found that the WBC counts were lower in the periodontitis group by

Table 3 Covid-19 complications.

	Periodontitis group	Non-periodontitis group
WARD		
Percent	12.23 %	3.72 %
ICU percent	3.19 %	0.00 %
Death		
Percent	1.60 %	0.00 %

Table 4 Laboratory test in covid-19 patients.

	Periodontitis group	Non-periodontitis group
WBC[AP22]		
Median	5.55	6.05
Range	3.99	4.02
HbA1c		
Median	5.85	5.50
Range	1.80	0.50
CRP		
Median	57.50	8.00
Range	84.00	13.00
ESR		
Median	40.00	32.00
Range	33.00	50.00

a median of 5.55. In contrast, the concentration of HbA1c, CRP level, and ESR were higher in the periodontitis group.

3.4. Factors associated with COVID-19 complications

Table 5 shows that patients with periodontitis were 3-times more likely to have COVID-19 complications than those without periodontitis ($p = 0.025$). Patients with comorbidities, diabetes ($p = 0.004$), or hypertension ($p = 0.016$) were 3.5-times more likely to have COVID-19 complications. The multivariate model exhibited reasonable power (C-statistic = 0.806).

4. Discussion

This study aimed to assess the possible relationship between periodontitis and COVID-19 severity. The results indicate, along with recently published studies, that COVID-19 complications are significantly higher among patients with periodontitis compared to those without periodontitis. Marouf et al. (2021) also found that periodontitis is associated with COVID-19 severity. In their case-control study, subjects were selected from national electronic health records to identify the influence of periodontitis on COVID-19 severity through different parameters. However, no statistical tests were performed to explore the influence of periodontitis in combination with systemic diseases on COVID-19 outcomes.

The oral cavity is considered an entry portal to many pathogens, including SARS-CoV-2, and this has been confirmed in the saliva of patients positive for COVID-19 (Arigbede et al., 2012). High viral load in the saliva has been noted at the beginning of infection, which resolves with COVID-19 resolution (Arigbede et al., 2012). The literature suggests that periodontitis and COVID-19 share similar inflammatory response pathways (Marouf et al., 2021; Sahni and Gupta, 2020). Periodontitis is

Table 5 Factors associated with covid-19 complications.

Variable	OR	95 % CI	p-value
Periodontitis (yes vs no)	3.063	1.150–8.157	0.025
Smoker (yes vs no)	1.648	0.436–6.230	0.461
Obese (yes vs no)	1.271	0.535–3.019	0.586
Diabetes (yes vs no)	3.543	1.489–8.432	0.004
Hypertension (yes vs no)	3.436	1.258–9.384	0.016

OR, odds ratio; CI, confidence interval.

a multifactorial disease that has been considered a source of systemic infection and a risk factor for systemic conditions, such as cardiovascular diseases, cerebrovascular diseases, and respiratory diseases (Arigbede et al., 2012; Kim and Amar, 2006). The possible link between periodontitis and respiratory diseases has been widely studied and multiple linking mechanisms reported. The first mechanism is the direct aspiration of periodontopathic bacteria into the lungs. The second mechanism is the secretion of hydrolytic enzymes by periodontal pathogens, which could inhibit the innate immune response by degrading cytokines and other inflammatory mediators released from periodontal tissues, altering the respiratory epithelium and resulting in enhanced adhesion of pathogens (Scannapieco and Mylotte, 1996; Sukumar and Tadepalli, 2021). In turn, this can cause infection to the lungs and increase the risk of secondary bacterial infection, especially in COVID-19 patients (Sukumar and Tadepalli, 2021).

Takahashi et al. (2020) suggested that the aspiration of periodontopathic bacteria in saliva may lead to overexpression of proinflammatory cytokines and angiotensin-converting enzyme 2 (ACE2) in the lower respiratory tract, aggravating COVID-19 symptoms. In addition, periodontopathic bacteria have been hypothesized to enhance SARS-CoV-2 virulence through cleavage of its S glycoproteins (Tay et al., 2020). Gupta and Sahni (2020) pointed out that both COVID-19 and periodontal disease share neutrophil extracellular trap production in their pathogenesis. These hypothetical theories may be a pathway for exploring the association observed between COVID-19 and periodontal disease, specifically, that the incidence of periodontal disease has increased during the pandemic (Sahni and Gupta, 2020). ACE2 and transmembrane protease serine 2 (TMPRSS2) are expressed in the sulcular epithelium and periodontal pocket epithelium (Kara et al., 2020). Recently, inhibiting TMPRSS2 has been shown to block SARS-CoV-2 invasion via ACE2, suggesting the possibility of SARS-CoV-2 infection via periodontal epithelium (Gupta and Sahni, 2020; Takahashi et al., 2020). The periodontal pocket has also been hypothesized to act as a favorable reservoir for SARS-CoV-2 in its active and latent forms (Scannapieco and Mylotte, 1996; Tay et al., 2020). A recent postmortem study identified the presence of SARS-CoV-2 RNA in the periodontal tissue of COVID-19 patients (Fernandes Matuck et al., 2021). In periodontal disease, inflamed gingival tissue undergoes immune cell-mediated pathogenesis with a greater level of cytokines, which systematically induce alterations in the serum cytokine levels (Sahni and Gupta, 2020; Scannapieco and Mylotte, 1996; Tang et al., 2020). Inflammatory markers, such as CRP, WBC, and neutrophils, are significantly higher in COVID-19 patients admitted to the ICU (Chen et al., 2020). In our study, the concentration of CRP was higher in patients with periodontitis. Chen et al. (2020) found that higher plasma CRP levels indicate serious COVID-19 pneumonia; higher CRP levels were noted in moderate to severe SARS-CoV-2 pneumonia patients. Gupta et al. (2022) found that poorer periodontal outcome measures correlate with increased CRP levels in patients suffering from COVID-19. In periodontitis, the host response to periodontal infections includes both innate and adaptive immunity (Paraskevas et al., 2008). Although periodontitis is considered a chronic disease, acute phase inflammatory markers of innate immunity are released, including CRP (Paraskevas et al., 2008). Previous studies evaluating CRP levels in periodontitis patients reported consistent

results on elevated levels in blood plasma (Goyal et al., 2014). Interestingly, the reason for the interest in studying CRP levels in patients with periodontitis is that CRP is related to cardiovascular disease, which could link periodontitis to cardiovascular disease (Paraskevas et al., 2008). Chronically elevated CRP levels in periodontitis patients exacerbate continuing inflammatory processes in atherosclerotic lesions, thereby increasing the risk of cardiovascular and cerebrovascular events (Paraskevas et al., 2008). In the current study, patients with periodontitis and systemic conditions, such as diabetes and hypertension, had a higher prevalence of COVID-19 complications. In line with these results, multivariate logistic regression modeling was carried out to adjust for possible confounders, including age, gender, and comorbidities.

Prior studies compared severely ill COVID-19 patients and moderately ill patients and concluded that patients with a more severe condition have higher concentrations of pro-inflammatory cytokines, which could result in poor disease outcomes (Tang et al., 2020). The immune response to SARS-CoV-2 infection results in an uncontrolled inflammatory response leading to cytokine storm (Tang et al., 2020). Cron and Behrens defined cytokine storm as an activation cascade of auto-amplifying cytokine production due to an unregulated host immune response to different triggers, including tumors and infections (Behrens and Koretzky, 2017). According to Sahni and Gupta (2020), the common pathway of the inflammatory responses from periodontitis and COVID-19 could be related to the severity of the latter.

The findings of the present study may be somewhat limited by the small sample size and missing data for smoking status and lab results. The diagnosis of periodontitis was assessed using panoramic radiographs and posterior bitewings regardless of the clinical measures (i.e., clinical attachment loss).

5. Conclusions

Periodontitis is significantly associated with a higher risk of developing COVID-19 complications, including the need for assisted ventilation, ICU admission, and death. Assessing the periodontal status can aid in identifying risk groups and reinforce the need to maintain optimal oral hygiene.

Ethics statement

This study was conducted in compliance with ICH-GCP ethical standards and research protocol #RSS 21R/012 /07 approved by institution review board (IRB) of King Abdullah International Medical Research Center (KAIMRC). All participants provided verbal consent .

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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