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Association between periodontitis and severity of COVID-19 infection: A case–control study

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Abstract

Aim: COVID-19 is associated with an exacerbated inflammatory response that can result in fatal outcomes. Systemic inflammation is also a main characteristic of periodontitis. Therefore, we investigated the association of periodontitis with COVID-19 complications.

Materials and Methods: A case–control study was performed using the national electronic health records of the State of Qatar between February and July 2020. Cases were defined as patients who suffered COVID-19 complications (death, ICU admissions or assisted ventilation), and controls were COVID-19 patients discharged without major complications. Periodontal conditions were assessed using dental radiographs from the same database. Associations between periodontitis and COVID 19 complications were analysed using logistic regression models adjusted for demographic, medical and behaviour factors.

Results: In total, 568 patients were included. After adjusting for potential confounders, periodontitis was associated with COVID-19 complication including death (OR = 8.81, 95% CI 1.00–77.7), ICU admission (OR = 3.54, 95% CI 1.39–9.05) and need for assisted ventilation (OR = 4.57, 95% CI 1.19–17.4). Similarly, blood levels of white blood cells, D-dimer and C Reactive Protein were significantly higher in COVID-19 patients with periodontitis.

Conclusion: Periodontitis was associated with higher risk of ICU admission, need for assisted ventilation and death of COVID-19 patients, and with increased blood levels of biomarkers linked to worse disease outcomes.

KEYWORDS
Covid-19, death, ICU admissions, periodontitis, ventilation

1 | INTRODUCTION

Coronavirus SARS-CoV-2 is a strain of the severe acute respiratory syndrome-related coronavirus (SARr-CoV), member of the Coronaviridae family and the responsible agent of the disease referred as 2019 coronavirus disease (COVID-2019). This emerging respiratory tract infection has resulted in over 75 million confirmed cases and almost 1.6 million deaths as of Dec 22th, 2020 (WHO, 2020b).

While most patients with COVID-19 present mild symptoms (Huang et al., 2020), nearly 14% of confirmed cases develop severe conditions requiring hospitalization and oxygen support, 5% need

admission to intensive care units and around 2% die (NCPERE, 2020). Severe cases are usually complicated by acute respiratory distress syndrome (ARDS), sepsis and septic shock, leading to multi-organ damage (Yang, Yu, et al., 2020). Patients with severe COVID-19 and ARDS (Mehta et al., 2020) usually present an exacerbated immune response, characterized by excessive levels of proinflammatory cytokines and widespread tissue damage; the so-called *cytokine storm syndrome* (Yang, Shen, et al., 2020). In fact, COVID-19 mortality has been associated with elevated serum levels of interleukin-6 (IL-6), C Reactive Protein (CRP), D-dimer and ferritin (Chen et al., 2020; Ruan et al., 2020), suggesting a clear link between disease severity and a virally driven non-resolving hyperinflammation.

Furthermore, COVID-19 infection severity has been associated with patients suffering comorbidities (e.g. hypertension, diabetes, cardiovascular disease) (Wu et al., 2020), older age and obesity (Zhou et al., 2020). However, the specific risk factors leading to poorer clinical outcomes have not been well fully elucidated.

The role of the oral cavity in COVID-19 has been controversial. While recent evidence suggests a relevant role of the oral mucosa in the transmission and pathogenicity of SARS-CoV-2 (Xu et al., 2020), the exposure of oral disease as a risk of increased severity of COVID-19 has not been demonstrated. Periodontitis is one of the most prevalent chronic inflammatory noncommunicable diseases (NCDs) (Eke et al., 2015). The Global Burden of Disease (GBD) Study and other epidemiological studies have reported that 50% of adults are affected by mild-to-moderate periodontitis, and 10% by the severe form of the disease, rendering it the sixth most prevalent condition affecting mankind (Petersen & Ogawa, 2012; Kassebaum et al., 2014). Severe periodontitis is characterized by destruction of the tooth attachment apparatus (Slots, 2017), and tooth loss if left untreated. This disease is characterized by chronic non-resolving inflammation in response to a dysbiosis in the subgingival biofilm (Curtis et al., 2020). The chronic inflammation frequently leads to low degree systemic inflammation and increased levels of cytokines, such as Tumour Necrosis Factor-α (TNF-α), Interleukin (IL)-1β, IL-4, IL-6 and IL-10 (Chapple et al., 2013; Acharya et al., 2017), as well as CRP and ferritin (Thounaojam, 2019).

Epidemiologic, experimental and interventional studies have shown that periodontitis may also impact systemic health. In fact, periodontitis has been independently associated with several NCDs, such as diabetes, cardiovascular diseases and even premature mortality (Sanz et al., 2018; Genco & Sanz, 2020; Romandini et al., 2020; Sanz et al., 2020). Periodontitis shares many risk factors with other NCDs, such as smoking, stress, unhealthy diet, glycaemic control, or genetic and socio-economic determinants (Pihlstrom et al., 2005; Petersen & Ogawa, 2012). However, specific mechanisms and pathological pathways have been identified directly linking periodontitis to these comorbidities, such as translocation of pathogens to blood (e.g. bacteraemia), systemic inflammation, and induced autoimmune damage (Schenkein, Papapanou, Genco, & Sanz, 2020).

Moreover, there is evidence that periodontal treatment leads to an improvement of glycaemic control in patients with type 2 diabetes (Teeuw et al., 2010), and metabolic syndrome (Montero et al., 2020), as well as improved renal function associated with diabetes (Chambrone et al., 2013). Periodontitis treatment also improves the balance of lipids and glucose metabolism (Teeuw et al., 2014), and biomarkers associated to atherosclerosis, such as serum CRP, IL-6, fibrinogen and IL-1 β levels (D'Aiuto et al., 2013; Tonetti et al., 2007).

Even though periodontitis and COVID-19 have both been associated with many common comorbidities, there is no evidence of a possible direct association between these two diseases. It was, therefore, the aim of this case–control study to estimate the extent to which periodontitis is associated with COVID-19 complications.

Clinical Relevance

Scientific rational for study: COVID-19 complications are caused by a severe inflammatory reaction that shares some common signals with periodontitis. Thus, this study was designed to investigate a possible association between COVID-19 complications and the presence of periodontitis.
Principle findings: This study revealed that periodontitis could be a risk factor for COVID-19 complications.
Practical implications: This study helps understand better the risk factors influencing the outcome of COVID-19 infections and highlights the importance of periodontal health in the prevention and perhaps even management of COVID-19 complications.

2 | METHODS

2.1 | Study population

Patients diagnosed with COVID-19 were selected from the national electronic health records at of Hamad Medical Corporation (HMC) in the State of Qatar. This corporation provides public health and dental coverage to the entire country and includes 14 hospitals holding approximately 85% of its hospital bed capacity. HMC has a single electronic health record system (Cerner, Kansas City, USA), in which each patient retains a unique hospital identification number for both the medical and dental records. Every patient with confirmed COVID-19 diagnosis according to the WHO interim guidelines (WHO, 2020a) and two subsequent positive PCR test for SARS-CoV-2 were included from 27 February 2020, the first date of a recorded COVID-19 diagnosis in Qatar, until 31 July 2020, if fulfilling the following inclusion criteria:

Adults (≥18 years old) discharged or deceased due to COVID-19 before the study end-date (31 August 2020), and with active dental records at Hamad Dental Services (HMC), with at least one dental appointment during the year preceding the Pandemic (March 2019 to March 2020). Patients with no dental radiographs in the records were excluded because the presence of periodontitis could not be objectively confirmed. Also, patients under the age of 18 were

excluded because they are unlikely to develop neither COVID-19 complications nor periodontitis.

2.2 | Study design

This case–control study of COVID-19 outcomes assessing periodontal status as exposure was approved by the Institutional Review Board of Hamad Medical Corporation with a waiver of informed consent under a pandemic response framework adopted by the institution.

Cases were defined as patients with registered COVID-19 complications in their records including death, ICU admissions or need of assisted ventilation due to COVID-19. Controls were defined as COVID patients discharged without major complications. No matching for controls was performed as all controls were included for analysis.

Our main exposure variable (periodontitis) and covariates (e.g. demographics, medical conditions), and outcomes of COVID-19 were extracted from the electronic health records at the Business Intelligence Center of Hamad Medical Corporation. The periodontal status was studied from posterior bitewings and panoramic radiographs in the patient's electronic records, using the XELIS Dental 1.0, Dental 3D INFINITT PACS® software. Interdental bone loss was measured in the posterior sextants using as reference the cement-enamel junction (CEJ) and the total length of the root. 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). When both bitewings and OPGs were available, the image with higher percentage of bone loss was selected.

Periodontitis was defined when bone loss was detected at 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. In light of the low sensitivity of panoramic and/or bite wing radiographs for slight bone crestal changes (Hellen-Halme et al., 2020), patients were categorized as follows (Tonetti et al., 2018):

- Periodontally healthy or initial periodontitis (Stages 0–1): Bone loss less than the coronal third of the root length (15%) in OPGs, or ≤2 mm in bitewing radiographs.
- Periodontitis (Stages 2–4): Bone loss more than the coronal third of the root length (>15%) in OPGs, or >2 mm in bitewing radiographs.

Each radiograph was assessed by two blinded investigators (N.M., H.D.). In case of discrepancy, a third blinded investigator (K.S.) reviewed the radiographs, and the majority diagnosis was considered. Investigators (N.M. H.D., K.S. and M.S.) were calibrated before the study reaching a kappa index of 90%.

We also obtained information on demographic (sex and age) and other relevant risk factors associated with COVID-19 complications, such as body mass index (BMI, kg/m^2), smoking habits, asthma, other chronic respiratory disease, chronic heart disease, diabetes, dermatitis, chronic liver disease, common autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus or psoriasis), solid organ transplant, peptic ulcer, immunosuppressive conditions, cancer, chronic kidney disease, hypertension, cerebrovascular accident, peptic ulcer and deep vein thrombosis. These conditions were determined by the presence of at least one ICD-10 code related to the above conditions in the patients record prior to the onset of the pandemic.

BMI was categorized as overweight/obese (BMI ≥ 25) and adequate/underweight (BMI < 25), smoking was categorized as current/past, and never smokers, and diabetes as present or absent. For the other chronic conditions, we created a variable "comorbidity" by computing the presence of each of the above condition. The values of this variable ranged from 0 to 7; we further categorized the variable according to number of comorbidity into 0, 1, and ≥2 because of low numbers in some of the categories.

Blood parameters relevant to the course of the disease such as concentrations of D-Dimer, CRP, HbA1c, Vitamin D, white blood cells (WBC) and lymphocytes were also collected from the electronic records. Both the initial parameters measured upon diagnosis as well as the latest parameters measured prior to discharge were collected.

2.3 | Sample size calculation and data analysis

A priori sample size calculation for logistic regression was used to determine the target sample size. For a minimum of four predictors, an expected R of 0.3, and a significance level set at α=0.05, a minimum sample size of n = 320 was determined to be needed to achieve an 80% power. The association between periodontitis and COVID-19 severity was analysed using logistic regression and data were reported as odds ratios (OR) and 95% confidence intervals (CIs). All models were adjusted for possible confounders including age, sex, smoking, BMI, diabetes and comorbidities. While age was used as a continuous variable, the remaining variables were categorical or binary variables. Additional sensitivity analyses were preformed by stratifying the data according to age groups, diabetes and smoking.

Laboratory values were assessed for normality and compared between groups using Mann and Whitney test. Statistical analyses were done using SPSS, version 20.0.

3 | RESULTS

3.1 | Characteristics of COVID-19 patients

From the 1076 patients identified with COVID-19 diagnosis and active dental records, 443 were excluded due to either lack of dental radiographs or relevant medical information. Furthermore, 65 patients were excluded for being <18 years of age. A total of 568 COVID-19-positive patients were included for the analysis. Among these, 40 experienced COVID complications (cases) and 528 were discharged without any complications (controls).

Table 1 displays the frequency distribution of the selected characteristics the study population. There was an equal sex distribution among COVID 19 patients with and without complications. As expected, patients with COVID-19 complications were older (mean 53.5 vs 41.5) and had more comorbidities than those without any complication. Similarly, more than 80% of all patients who had COVID-19 complications had periodontitis compared to only 43% of those without COVID-19 complications.

Table 2 reports the association between COVID-19 severity, and the laboratory biomarker data studied. A total of 197 patients had laboratory records for HbA1c, 177 for Vit-D, 96 for D-Dimer, 394 for lymphocytes, 397 for WBC and 310 for CRP. Assessment of the latest laboratory records revealed that the concentrations of D-dimer, WBC and CRP were significantly higher in COVID-19-deceased patients when compared with surviving patients. On the other hand, the concentrations of lymphocytes were significantly lower in the deceased patients. Patients admitted to the ICU as well as patients requiring assisted ventilation also had significantly higher D-dimer, WBC and CRP serum levels than patients that did not enter the ICU or those that did not require assisted ventilation, respectively.

3.2 | Periodontal conditions of COVID-19 patients

Out of the 568 patients included in our study, a 258 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 3 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.

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 (Tables S1-S4), 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 (Table S3). In addition, periodontitis was also significantly associated with need for ventilation among non-smokers (Table S4).

TABLE 1 Selected characteristics of the cases and controls

	Controls	Cases			
	COVID 19 patients without complications (*n* = 528)	All complications (*N* = 40)	Death *N* = 14 (%)	ICU admission *N* = 36 (%)	Assisted ventilation *N* = 20 (%)
Sex					
Male	290 (54.9)	20 (50.0)	7 (50.0)	17 (47.2)	10 (50.0)
Female	238 (45.1)	20 (50.0)	7 (50.0)	19 (52.8)	10 (50.0)
Age					
Mean, years (SD)	41.5 (14.1)	53.6 (15.0)	56.6 (17.6)	52.8 (15.4)	53.3 (15.7)
Smoker					
Never	460 (87.1)	29 (72.5)	8 (57.1)	28 (77.8)	15 (75.0)
Past/current	68 (12.9)	11 (27.5)	6 (42.9)	8 (22.2)	5 (25.0)
Diabetes					
Yes	147 (27.8)	17 (42.5)	8 (57.1)	20 (55.6)	12 (60.0)
No	381 (42.9)	23 (57.5)	6 (42.9)	16 (44.4)	8 (40.0)
Comorbidity					
None	314 (59.5)	5 (12.5)	0 (0)	5 (13.9)	3 (15.0)
One comorbidity	103 (19.5)	11 (27.5)	4 (28.6)	10 (27.8)	5 (25.0)
Two comorbidities	111 (21.0)	24 (60.0)	10 (71.4)	21 (58.3)	12 (60.0)
BMI					
Adequate weight (≥25)	119 (24.5)	6 (20.0)	3 (42.9)	5 (17.9)	366 (75.5)
Overweight/Obese (<25)	366 (75.5)	24 (80.0)	4 (57.1)	23 (82.1)	11 (73.3)

TABLE 2 laboratory data of deceased patients compared to surviving ones

	Surviving patients			Deceased patients			
Laboratory parameter[b]	***n***	**Median**	**Range**	***n***	**Median**	**Range**	***p*[a]**
HbA1c (%)	191	5.8	10.6	6	7.4	18.8	0.445
Vit-D (ng/ml)	173	22.0	168.0	4	12.33	34.2	0.144
D_Dimer (mg/L)	84	0.475	11.82	12	5.42	288.5	**0.001**
Lymphocyte (10^3/μl)	382	2.0	5.5	12	0.65	9.9	**0.005**
WBC (10^3/μl)	385	5.8	12.7	12	14.45	131.7	**0.001**
CRP (mg/L)	300	5.75	338.1	10	52.15	323.1	**0.001**
	Non-ICU patients			**ICU patients**			
	n	**Median**	**Range**	***n***	**Median**	**Range**	
HbA1c (%)	172.0	5.7	7.2	25.0	6.2	18.8	0.098
Vit-D (ng/ml)	161.0	22.0	168.0	16.0	17.5	37.6	0.110
D_Dimer (mg/L)	65.0	0.5	5.1	30.0	1.1	288.8	**0.003**
Lymphocyte (10^3/μl)	363.0	2.0	5.5	30.0	1.7	9.9	0.155
WBC (10^3/μl)	364.0	5.7	67.2	32.0	7.6	131.7	**<0.001**
CRP (mg/L)	281.0	5.4	338.1	28.0	24.3	87.1	**<0.001**
	No ventilation			**Ventilation patients**			
	N	**Median**	**Range**	***n***	**Median**	**Range**	
HbA1c (%)	185	5.7	10.6	12	6.2	18.8	0.370
Vit-D (ng/ml)	168	22.0	168.0	9	21.0	19.2	0.174
D_Dimer (mg/l)	78	0.5	5.4	18	2.3	288.7	**<0.001**
Lymphocyte (10^3/μl)	376	2.0	5.5	18	1.6	9.9	0.180
WBC (10^3/μl)	378	5.8	67.2	19	7.0	131.7	**0.045**
CRP (mg/l)	294	5.8	345.2	16	25.2	87.1	**0.010**

[a]Mann–Whitney test; *p* values <0.05 were considered statistically significant.

[b]The laboratory values correspond to the latest laboratory parameters measured.

Table 4 describes the association between periodontal status and the surrogate laboratory biomarkers studied. HbA1c, WBC and CRP blood levels were significantly higher in COVID-19 patients with periodontal disease than in those without periodontal disease.

4 | DISCUSSION

This study identified that the risk of COVID-19 complications was significantly higher among patients with moderate-to-severe periodontitis compared to those with milder or no periodontitis. Periodontitis shares common risk factors with most chronic inflammatory diseases known to influence COVID-19 severity (Ruan et al., 2020; Zhou et al., 2020); thus, we performed multivariate logistic regression modelling to adjust this association for possible confounders such as age, sex, and smoking behaviour, and for comorbidities (diabetes, hypertension, etc.). After adjustment, periodontitis still had a significant impact on the course of COVID-19 infection, with significant associations COVID 19 complications (OR = 3.67, 95% CI 1.46–9.27), death (OR =8.81, 95% CI 1.00–77.7), ICU admission (OR = 3.54, 95% CI 1.39–9.05) and need for assisted ventilation (OR = 4.57, 95% CI 1.19–17.4). These compelling results further confirm the association between periodontitis and worse progression of COVID-19.

Periodontitis has been shown to affect systemic health in multiple studies (Monsarrat et al., 2016) and has been independently associated with increased risk of most chronic NCDs (Genco & Sanz, 2020), in particular cardiovascular diseases (Tonetti & Van Dyke, 2013; LaMonte et al., 2017; Sanz et al., 2020); diabetes (Chapple et al., 2013; Suvan et al., 2015; Sanz et al., 2018); hypertension (Munoz Aguilera et al., 2020); chronic renal disease (Sharma et al., 2016), pneumonia (Gomes-Filho et al., 2020) and cancer (Nwizu et al., 2020). Furthermore, a recent systematic review of 57 studies with 5.71 million participants reported the association of periodontitis with increased risk of mortality, specifically, in association with CVD, cancer, CHD and cerebrovascular diseases (Romandini et al.,

TABLE 3 Associations between periodontal condition and COVID-19 complications

	Controls (*n* = 528)	Cases: All COVID complications (*n* = 40)		
Periodontal condition			**Unadjusted OR (95% CI)**	**AOR[a] (95% CI)**
Stage 0–1	303 (57.4)	7 (17.5)	1	1
Stage 2–4	225 (42.8)	33 (82.5)	6.34 (2.79–14.61)	3.67 (1.46–9.27)
		Cases: death (*n* = 14)		
Stage 0–1	303 (57.4)	1 (7.1)	1	1
Stage 2–4	225 (42.8)	13 (92.9)	17.5 (2.27–134.8)	8.81 (1.00–77.7)
		Cases: ICU admission (*n* = 36)		
Stage 0–1	303 (57.4)	7 (19.4)	1	1
Stage 2–4	225 (42.8)	29 (80.6)	5.57 (2.40–12.9)	3.54 (1.39–9.05)
		Cases: need for assisted ventilation (*n* = 20)		
Stage 0–1	303 (57.4)	3 (15.8)	1	1
Stage 2–4	225 (42.8)	17 (85.0)	7.31 (2.21–26.3)	4.57 (1.19–17.4)

[a]Adjusted to age, sex, diabetes, comorbidity, smoking behaviour.

TABLE 4 Laboratory data of patients with periodontal disease compared to surviving ones.

	Laboratory parameters					
	HbA1c (%)	**Vit-D (ng/ml)**	**D-Dimer (mg/L)**	**Lymphocyte (10^3/µl)**	**WBC (10^3/µl)**	**CRP (mg/L)**
Initial measurements						
Stage 0–1						
N	85	87	34	203	204	158
Median	5.5	18.5	0.45	1.83	5.34	4.95
Range	5.1	60	4.21	5.21	10.9	176.4
Stage 2–4						
N	112	90	62	191	193	152
Median	6.15	23	0.56	1.69	5.9	7.4
Range	10.5	168	10.67	5	24	340.8
p[a]	**<0.001**	**0.024**	0.494	0.056	0.056	**0.001**
latest measurements						
Stage 0–1						
Median	5.5	22	0.51	2.0	5.47	4.05
Range	5.1	66	7.72	4.2	11.3	221.7
Stage 2–4						
Median	6.2	23	0.51	2.0	6.2	8.1
Range	18.8	168	288.81	9.9	131.7	345.2
p[a]	**<0.001**	0.135	0.45	0.766	**0.005**	**<0.001**

[a]Mann–Whitney test; *p* values <0.05 were considered statistically significant.

2020). These associations have been explained, by shared genetic and environmental risk factors, and also through common chronic inflammatory pathways (Schenkein et al., 2020).

Several hypothetical mechanisms may explain the strong associations observed between periodontitis and COVID-19 severity. Takahashi *et al* suggested that aspiration of periodontopathic bacteria might aggravate COVID-19 by inducing the expression of angiotensin-converting enzyme 2, a receptor for SARS-CoV-2, and inflammatory cytokines in the lower respiratory tract (Takahashi et al., 2020). Also, it was suggested that periodontopathic bacteria might enhance SARS-CoV-2 virulence by cleaving its S glycoproteins (Madapusi Balaji et al., 2020; Takahashi et al., 2020) and that the oral cavity, and specially periodontal pockets could act as a viral reservoir (Badran et al., 2020; Bao et al., 2020; Botros et al., 2020; Herrera et al., 2020; Kheur et al., 2020). Gupta *et al* indicated that Neutrophil Extracellular Trap production is involved in the pathogenesis of both diseases (Gupta & Sahni,

2020), and Sahni *et al* suggested that the strong Th17 response in severe periodontitis could exacerbate the cytokine storm in COVID-19 (Sahni & Gupta, 2020). All these hypothetical pathways could also foresee an increased incidence of periodontal lesions, especially necrotizing periodontal disease (NPD) during this pandemic (Patel & Woolley, 2020).

In our study, fatal COVID-19 outcomes were significantly associated with higher blood concentrations of D-dimer, WBC and CRP, and lower concentrations of lymphocytes. Also, patients admitted to the ICU as well as those requiring assisted ventilation presented high blood levels of CRP and D-dimer. These results are in agreement with previous studies reporting elevated inflammatory indicators in deceased COVID-19 patients (Ruan et al., 2020). Interestingly, our COVID-19 cases with periodontitis also had significantly higher WBC and CRP serum levels than those without periodontitis, which may indicate a possible link of this association through systemic inflammation.

Successful treatment of periodontitis has been shown to improve serum markers of systemic inflammation (CRP, IL-6) (D'Aiuto et al., 2013), as well as systemic metabolic control (Montero et al., 2020). If a causal link is established between periodontitis and increased rates of adverse outcomes in COVID-19 patients, then establishing and maintaining periodontal health may become an important part of the care of these patients.

This cross-sectional study has clear limitations, and the results need to be taken with caution. It does not address causality, and even though we adopted the new classification for staging Periodontitis (Papapanou et al., 2018), using only one of the parameters (interdental bone loss) may limit the diagnostic accuracy. Nonetheless, this was mitigated by blinded assessment of the radiographs by independent examiners. Regarding statistical power, a representative sample was recruited, based on all COVID-19 cases registered in the country from the beginning of the COVID-19 pandemic, which also reduced selection bias.

Future research, including interventional studies focused on the influence of periodontitis and periodontal treatments on COVID-19 infections, would help better understand the causal connections between them. Furthermore, understanding the mechanisms underpinning the relationship between periodontitis and COVID-19 complications is a promising area of research that may produce mechanistic targets, risk stratification and novel interventions.

5 | CONCLUSION

Periodontitis was significantly associated with a higher risk of complications from COVID-19, including ICU admission, need for assisted ventilation and death and increased blood levels of markers linked worse COVID-19 outcome such as D-dimer, WBC and CRP.

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ETHICAL APPROVAL

This study was conducted after obtaining expedited review and approval from the Institutional Review Board of Hamad Medical Corporation with the study number: MRC-05-092.

CONFLICT OF INTEREST

The authors declare no conflict of interest relevant to this study.

AUTHOR CONTRIBUTIONS

F.T., B.N., W.C., M.S., K.N., N.M. and A.H. contributed towards the conception of the study. F.T. and A.H. obtain ethical approval. H. Daas, H. Diab, K.N., V.C. and N.M contributed towards the data extraction. W.C., B.N. and F.T. contributed towards the data analysis. M.S., B.N and F.T. contributed towards the data interpretation. A.H., M.S. B.N., K.N. and F.T. drafted the work and revised it critically for important intellectual content. All authors gave final approval of the published version and agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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