



# Association of periodontal therapy, with inflammatory biomarkers and complications in COVID-19 patients: a case control study

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## Abstract

**Background** In previous studies, COVID-19 complications were reported to be associated with periodontitis. Accordingly, this study was designed to test the hypothesis that a history of periodontal therapy could be associated with lower risk of COVID-19 complications.

**Methods** A case–control study was performed using the medical health records of COVID-19 patients in the State of Qatar between March 2020 and February 2021 and dental records between January 2017 and December 2021. Cases were defined as COVID-19 patients who suffered complications (death, ICU admissions and/or mechanical ventilation); controls were COVID-19 patients who recovered without major complications. Associations between a history of periodontal therapy and COVID-19 complications were analysed using logistic regression models adjusted for demographic and medical factors. Blood parameters were compared using Kruskal–Wallis test.

**Results** In total, 1,325 patients were included. Adjusted odds ratio (AOR) analysis revealed that non-treated periodontitis was associated with significant risk of need for mechanical ventilation (AOR = 3.91, 95% CI 1.21–12.57,  $p = 0.022$ ) compared to periodontally healthy patients, while treated periodontitis was not (AOR = 1.28, 95% CI 0.25–6.58,  $p = 0.768$ ). Blood analyses revealed that periodontitis patients with a history of periodontal therapy had significantly lower levels of D-dimer and Ferritin than non-treated periodontitis patients.

**Conclusion** Among COVID-19 patients with periodontal bone loss, only those that have not received periodontal therapy had higher risk of need for assisted ventilation. COVID-19 patients with a history of periodontal therapy were associated with significantly lower D-dimer levels than those without recent records of periodontal therapy.

**Clinical relevance** The fact that patients with treated periodontitis were less likely to suffer COVID-19 complications than non-treated ones further strengthen the hypothesis linking periodontitis to COVID-19 complications and suggests that managing periodontitis could help reduce the risk for COVID-19 complications, although future research is needed to verify this.

**Keywords** Periodontitis · Periodontal disease · COVID-19 · Periodontal therapy · D-dimer

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## Introduction

The coronavirus disease of 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS Cov-2) has compromised the well-being of individuals and health-care systems worldwide [1, 2]. COVID-19 is mostly mild or asymptomatic, but, in some patients, it can cause severe complications and even death [3, 4]. These complications are associated with an exacerbated inflammatory response called the “cytokine storm”, which is characterized by lymphocytopenia, neutrophilia, coagulopathies and increased blood levels of inflammatory cytokines [5–7]. COVID-19 complications are associated to certain risk factors (i.e. age, gender (male), obesity, hypertension, cardiovascular disease (CVD), cerebrovascular disease (CVD), chronic kidney disease and diabetes [8]) that have also been linked to periodontitis [9]. This has prompted the study of a possible association between periodontitis and COVID-19 severity [10]. Indeed, a study from our group has shown a significant association between periodontal bone loss and increased risk of COVID-19 complications [11], other groups have reported that poor oral health correlates significantly with COVID-19 severity [12, 13], and another study has shown that periodontitis could exacerbate the negative impact of obesity on COVID-19 [14].

Besides the association between periodontitis and the medical conditions described above, intervention trials and observational studies have also demonstrated that periodontal therapy may significantly reduce the risk of these conditions. For instance, recent systematic reviews have shown a reduction in HbA1c and fasting plasma glucose after periodontal treatment and could prevent diabetic complications [9, 15]. Similarly, randomized controlled trials have shown that periodontal therapy can reduce serum inflammatory mediators and induce positive changes in surrogate measures of atherothrombosis [16]. Moreover, recent population-based studies using medical registries have demonstrated that oral care interventions such as frequent tooth brushing and professional cleaning were associated with lower cardiovascular risk [17].

These associations have led us to hypothesize that periodontal care could also play a role in preventing COVID-19 complications. It was, therefore, the purpose of this study to evaluate the impact of periodontal treatment on the occurrence of COVID-19 complications.

## Material and methods

Ethical approval for this retrospective case–control study was obtained from the Institutional Review Board of Hamad Medical Corporation (HMC) with a waiver of

informed consent under the pandemic response framework (protocol number MRC-01–20-1228). The study was conducted according to the STROBE guidelines.

## Study population

This is an expansion on our previous study in terms of scope and sample size [11]. Adult subjects (18 years and older) were selected from the electronic records of HMC based on a confirmed COVID-19 diagnosis between March, 1st 2020, and December, 31st, 2020. To assess the disease outcome, COVID-19 data on these patients was extracted until February 28th, 2021. Both hospitalized and out-patient records were included.

HMC is the sole provider of medical care for COVID-19 patients in Qatar, a service provided free of charge to all patients in the country. Moreover, in Qatar, regular medical and dental care are offered free of charge for citizens and at significantly low cost for non-citizens in the public health-care system. The medical and dental electronic records are linked through a unique hospital identification number for every patient.

All COVID-19 patients with active medical and dental records at HMC, including panoramic radiographs taken between January, 1st, 2017, and December, 31st, 2021, were included. Exclusion criteria were young age (less than 18 years of age) and lack of dental records. The COVID-19 vaccination records of the country were also searched to assess the vaccination status of the patients prior to their COVID-19 infection.

## Study design

Cases were defined as patients that experienced COVID-19-related complications such as ICU admission, mechanical ventilation and/or death. Controls were COVID-19 patients that recovered without major complications. All controls were included for analysis and no matching was performed.

All medical data from cases and controls including COVID-19 outcomes, predisposing conditions and blood sample analysis were extracted from HMC electronic records as described previously [11]. Information on predisposing conditions included patient’s sex, age, body mass index (BMI, kg/m<sup>2</sup>), smoking habits, asthma, chronic respiratory diseases, chronic heart disease, diabetes, dermatitis, chronic liver disease, autoimmune diseases, solid organ transplant, peptic ulcer, immunosuppressive conditions, cancer, chronic kidney disease, hypertension, cerebrovascular accidents and deep vein thrombosis.

Blood biomarkers analysed included D-dimer, C-reactive protein (CRP), urea, creatinine, ferritin, interleukin-6 (IL-6),

HbA1c, vitamin D, white blood cells (WBC) and lymphocytes. Both the initial blood tests taken upon COVID-19 diagnosis and the latest parameters measured prior to discharge were included for both cases and control patients.

The periodontal status was assessed on patient's panoramic radiographs by measuring inter-dental bone loss in posterior teeth using the criteria of the 2017 classification of periodontal diseases [18]. Periodontal bone loss was defined as bone loss at two or more non-adjacent teeth after excluding local factors (periodontal-endodontic lesions, cracked and fractured roots, caries, restorative factors and impacted third molars). Given the low sensitivity of panoramic radiographs [19], patients were categorized into two groups [20]: (i) non-to-mild periodontal bone loss (stages 0–1): bone loss  $\leq 15\%$  of the root length; and (ii) moderate-to-severe periodontal bone loss (stages 2–4): bone loss  $> 15\%$  of the root length. To assess differences in bone loss severity across groups, we compared the actual percentage of interdental bone loss at posterior teeth. Each radiograph was assessed by two blinded investigators. In case of discrepancy, a third blinded investigator reviewed the radiographs, and the majority diagnosis was considered. All examiners were calibrated before the beginning of the study using two sets of 20 radiographs each, 14 days apart reaching a kappa index of 85%.

Patients were considered to have received periodontal treatment if they had radiographic signs of periodontal bone loss and at least one periodontal therapy procedure documented in their records for either non-surgical (i.e., scaling, root planing and polishing) or surgical periodontal treatment (i.e., periodontal flap procedure, regenerative therapy, osseous surgery, gingivectomy) between January, 1st, 2019, and December, 31st, 2020. Only periodontal treatments conducted before the subject was diagnosed with COVID-19 infection were considered for this investigation. To validate the radiographic assessment of periodontitis and the effectiveness of periodontal treatments, we analysed the subset of dental records within the cohort of patients followed at the Division of Periodontics at HMC. Response to periodontal therapy was reported in the dental records as changes in probing depth, reduced bleeding on probing, improved attachment level and reduced plaque levels.

Hospitalized patients with COVID-19 were assessed for respiratory bacterial infections if clinical signs of infection were compatible with laboratory and imaging findings. Respiratory specimens were collected by either endotracheal aspirate or bronchoalveolar lavage, and bacterial pathogens were defined using standard culture methods.

## Data analysis

Sample size was calculated to obtain 80% power with  $\alpha$ -error of 0.05, and effect size  $f^2$  of 0.10 and 10 predictors

based on our previous study [11]. An estimated sample size of at least 172 subjects per group was found to be needed to compare COVID-19 complications between periodontally healthy and patients with periodontal bone loss who were not treated for periodontitis.

The association between periodontal bone loss, periodontal therapy and COVID-19 severity was analysed using logistic regression models adjusted for confounders including age, sex, smoking, BMI, citizenship, diabetes and co-morbidities. Age was used as a continuous variable, BMI was categorized as overweight/obese ( $\text{BMI} \geq 25$ ) and adequate/underweight ( $\text{BMI} < 25$ ), and smoking was categorized as current/past and never smokers. Given the low prevalence of other comorbidities, we created a comorbidity score as proposed elsewhere [21]. This comorbidity score included hypertension, asthma, chronic respiratory disease, chronic heart disease, 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, cerebrovascular accident and deep vein thrombosis. For these conditions, a variable “comorbidity” was generated by computing the presence of each of the above conditions according to the number of comorbidities into 0, 1 and  $\geq 2$ . This comorbidity index was validated using an OR and Chi-square test, and it showed to be a very strong predictor of COVID-19 complications (Supp. Table 6). Logistic regression analyses were reported as adjusted odds ratios (AOR) with 95% confidence intervals (CIs). Periodontal bone loss (%) across groups was compared using two-way ANOVA with post hoc Bonferroni correction. Laboratory biomarkers were assessed for normality and compared across groups using Kruskal–Wallis test with Bonferroni correction for multiple testing. Differences were considered statistically for  $p < 0.05$ . Statistical analyses were done using SPSS (v20.0, SPSS, IBM, Armonk, NY).

## Results

Out of the 141,422 COVID-19 cases registered in Qatar by end of February 2021, 2,621 had active dental records; among these patients, 1247 were excluded for not having recent panoramic radiographs and 49 for not having posterior teeth suitable for periodontal assessment. Thus, 1,325 patients fulfilled the above-mentioned criteria and were included for analysis; none of these patients were vaccinated by the time of their SARS-CoV-2 infection. From these patients, 71 suffered severe COVID-19 complications resulting in ICU admission, mechanical ventilation and/or death. Patients with complications were more likely to be males, older, and suffering from comorbidities (Table 1).

**Table 1** Description of the study cohort according to the demographics, medical conditions and COVID-19 complications

| Conditions                 | No complications ( <i>n</i> = 1254) | Complications ( <i>n</i> = 71) | <i>p</i>                       |
|----------------------------|-------------------------------------|--------------------------------|--------------------------------|
| Age (median [IQR])         | 39.00 [30.00, 52.00]                | 50.00 [41.50, 61.50]           | <b>&lt; 0.001</b> <sup>a</sup> |
| BMI (median [IQR])         | 29.03 [25.22, 32.86]                | 29.88 [24.07, 35.48]           | 0.488 <sup>a</sup>             |
| Sex (%)                    |                                     |                                |                                |
| Female                     | 718 (57.2)                          | 30 (42.3)                      | <b>0.014</b> <sup>b</sup>      |
| Male                       | 536 (42.8)                          | 41 (57.7)                      |                                |
| Citizenship status (%)     |                                     |                                |                                |
| Non-Qatari citizen         | 573 (45.7)                          | 40 (56.3)                      | 0.080 <sup>b</sup>             |
| Qatari citizen             | 681 (54.3)                          | 31 (43.7)                      |                                |
| Smoking habits (%)         |                                     |                                |                                |
| Never smoker               | 1090 (86.9)                         | 59 (83.1)                      | 0.368 <sup>b</sup>             |
| Past/present smoker        | 164 (13.1)                          | 12 (16.9)                      |                                |
| Hypertension (%)           |                                     |                                |                                |
| No                         | 972 (77.5)                          | 31 (43.7)                      | <b>&lt; 0.001</b> <sup>b</sup> |
| Yes                        | 282 (22.5)                          | 40 (56.3)                      |                                |
| Diabetes (%)               |                                     |                                |                                |
| No                         | 894 (71.3)                          | 29 (40.8)                      | <b>&lt; 0.001</b> <sup>b</sup> |
| Yes                        | 360 (28.7)                          | 42 (59.2)                      |                                |
| Asthma (%)                 |                                     |                                |                                |
| No                         | 1091 (87.0)                         | 51 (71.8)                      | <b>0.001</b> <sup>b</sup>      |
| Yes                        | 163 (13.0)                          | 20 (28.2)                      |                                |
| Autoimmune (%)             |                                     |                                |                                |
| No                         | 1237 (98.6)                         | 71 (100.0)                     | 0.323 <sup>b</sup>             |
| Yes                        | 17 (1.4)                            | 0 (0.0)                        |                                |
| Cardiovascular (%)         |                                     |                                |                                |
| No                         | 1018 (81.2)                         | 27 (38.0)                      | <b>&lt; 0.001</b> <sup>b</sup> |
| Yes                        | 236 (18.8)                          | 44 (62.0)                      |                                |
| COPD (%)                   |                                     |                                |                                |
| No                         | 1247 (99.4)                         | 68 (95.8)                      | <b>0.001</b> <sup>b</sup>      |
| Yes                        | 7 (0.6)                             | 3 (4.2)                        |                                |
| Peptic ulcer (%)           |                                     |                                |                                |
| No                         | 1230 (98.1)                         | 67 (94.4)                      | <b>0.034</b> <sup>b</sup>      |
| Yes                        | 24 (1.9)                            | 4 (5.6)                        |                                |
| Cancer (%)                 |                                     |                                |                                |
| No                         | 1233 (98.3)                         | 57 (80.3)                      | <b>&lt; 0.001</b> <sup>b</sup> |
| Yes                        | 21 (1.7)                            | 14 (19.7)                      |                                |
| Chronic kidney disease (%) |                                     |                                |                                |
| No                         | 1230 (98.3)                         | 56 (78.9)                      | <b>&lt; 0.001</b> <sup>b</sup> |
| Yes                        | 24 (1.7)                            | 15 (21.1)                      |                                |
| Chronic liver disease (%)  |                                     |                                |                                |
| No                         | 1236 (98.6)                         | 61 (85.9)                      | <b>&lt; 0.001</b> <sup>b</sup> |
| Yes                        | 18 (1.4)                            | 10 (14.1)                      |                                |
| Dermatitis (%)             |                                     |                                |                                |
| No                         | 829 (66.1)                          | 38 (53.5)                      | <b>0.030</b> <sup>b</sup>      |
| Yes                        | 425 (33.9)                          | 33 (46.5)                      |                                |
| Organ transplant (%)       |                                     |                                |                                |
| No                         | 1249 (99.6)                         | 63 (88.7)                      | <b>&lt; 0.001</b> <sup>b</sup> |
| Yes                        | 5 (0.4)                             | 8 (11.3)                       |                                |

<sup>a</sup>Kruskal-Wallis rank sum test. <sup>b</sup>Pearson's Chi-squared test

**Table 2** Demographic characteristics of patients according to the presence and treatment of periodontitis

| Conditions                 | No periodontitis (n = 721) | Non-treated periodontitis (n = 417) | Treated periodontitis (n = 187) | p                             |
|----------------------------|----------------------------|-------------------------------------|---------------------------------|-------------------------------|
| Age (median [IQR])         | 33.00 [25.00, 41.00]       | 49.00 [39.00, 59.00]                | 51.00 [42.50, 58.00]            | <b>&lt; 0.001<sup>a</sup></b> |
| BMI (median [IQR])         | 28.00 [24.21, 32.05]       | 30.01 [26.43, 33.78]                | 29.76 [26.86, 33.75]            | <b>&lt; 0.001<sup>a</sup></b> |
| Sex (%)                    |                            |                                     |                                 |                               |
| Female                     | 464 (64.4)                 | 191 (45.8)                          | 93 (49.7)                       | <b>&lt; 0.001<sup>b</sup></b> |
| Male                       | 257 (35.6)                 | 226 (54.2)                          | 94 (50.3)                       |                               |
| Citizenship status (%)     |                            |                                     |                                 |                               |
| Non-Qatari citizen         | 290 (40.2)                 | 243 (58.3)                          | 80 (42.8)                       | <b>&lt; 0.001<sup>b</sup></b> |
| Qatari Citizen             | 431 (59.8)                 | 174 (41.7)                          | 107 (57.2)                      |                               |
| Smoking habits (%)         |                            |                                     |                                 |                               |
| Never smoker               | 653 (87.4)                 | 339 (81.3)                          | 157 (84.0)                      | <b>&lt; 0.001<sup>b</sup></b> |
| Past/present smoker        | 68 (12.6)                  | 78 (18.7)                           | 30 (16.0)                       |                               |
| Hypertension (%)           |                            |                                     |                                 |                               |
| No                         | 625 (86.7)                 | 246 (59.0)                          | 132 (70.6)                      | <b>&lt; 0.001<sup>b</sup></b> |
| Yes                        | 96 (13.3)                  | 171 (41.0)                          | 55 (29.4)                       |                               |
| Diabetes (%)               |                            |                                     |                                 |                               |
| No                         | 579 (80.3)                 | 227 (54.4)                          | 117 (62.6)                      | <b>&lt; 0.001<sup>b</sup></b> |
| Yes                        | 142 (19.7)                 | 190 (45.6)                          | 70 (37.4)                       |                               |
| Asthma (%)                 |                            |                                     |                                 |                               |
| No                         | 628 (87.1)                 | 354 (84.9)                          | 160 (85.6)                      | 0.561 <sup>b</sup>            |
| Yes                        | 93 (12.9)                  | 63 (15.1)                           | 27 (14.4)                       |                               |
| Autoimmune (%)             |                            |                                     |                                 |                               |
| No                         | 712 (98.8)                 | 413 (99.0)                          | 183 (97.9)                      | 0.488 <sup>b</sup>            |
| Yes                        | 9 (1.2)                    | 4 (1.0)                             | 4 (2.1)                         |                               |
| Cardiovascular (%)         |                            |                                     |                                 |                               |
| No                         | 636 (88.2)                 | 267 (64.0)                          | 142 (75.9)                      | <b>&lt; 0.001<sup>b</sup></b> |
| Yes                        | 85 (11.8)                  | 150 (36.0)                          | 45 (24.1)                       |                               |
| COPD (%)                   |                            |                                     |                                 |                               |
| No                         | 719 (99.7)                 | 410 (98.3)                          | 186 (99.5)                      | <b>0.029<sup>b</sup></b>      |
| Yes                        | 2 (0.3)                    | 7 (1.7)                             | 1 (0.5)                         |                               |
| Peptic ulcer (%)           |                            |                                     |                                 |                               |
| No                         | 713 (98.9)                 | 404 (96.9)                          | 180 (96.3)                      | <b>0.019<sup>b</sup></b>      |
| Yes                        | 8 (1.1)                    | 13 (3.1)                            | 7 (3.7)                         |                               |
| Cancer (%)                 |                            |                                     |                                 |                               |
| No                         | 710 (98.5)                 | 393 (94.2)                          | 187 (100.0)                     | <b>&lt; 0.001<sup>b</sup></b> |
| Yes                        | 11 (1.5)                   | 24 (5.8)                            | 0 (0.0)                         |                               |
| Chronic kidney disease (%) |                            |                                     |                                 |                               |
| No                         | 712 (98.8)                 | 390 (93.5)                          | 184 (98.4)                      | <b>&lt; 0.001<sup>b</sup></b> |
| Yes                        | 9 (1.2)                    | 27 (6.5)                            | 3 (1.6)                         |                               |
| Chronic liver disease (%)  |                            |                                     |                                 |                               |
| No                         | 710 (98.5)                 | 404 (96.9)                          | 183 (97.9)                      | 0.198 <sup>b</sup>            |
| Yes                        | 11 (1.5)                   | 13 (3.1)                            | 4 (2.1)                         |                               |
| Dermatitis (%)             |                            |                                     |                                 |                               |
| No                         | 491 (68.1)                 | 260 (62.4)                          | 116 (62.0)                      | 0.083 <sup>b</sup>            |
| Yes                        | 230 (31.9)                 | 157 (37.6)                          | 71 (38.0)                       |                               |
| Organ transplant (%)       |                            |                                     |                                 |                               |
| No                         | 718 (99.6)                 | 407 (97.6)                          | 187 (100.0)                     | <b>0.002<sup>b</sup></b>      |
| Yes                        | 3 (0.4)                    | 10 (2.4)                            | 0 (0.0)                         |                               |

<sup>a</sup>Kruskal-Wallis rank sum test. <sup>b</sup>Pearson's Chi-squared test. The statistical analysis was testing for differences between the three groups

Among the included patients, 721 had none-to-mild periodontitis (stages 0–1), while 604 had moderate-to-severe periodontitis (stages 2–4) (Table 2). A total of 833 periodontal non-surgical and surgical procedures were done in 381 patients before COVID-19 infection, between January 1st, 2019, and December 31st, 2020 (Supp. Table 5). Only 187 of the patients that received periodontal care fit the criteria of stage 2–4 periodontitis by showing radiographic signs of moderate to severe interdental bone loss.

On average, the percentage of periodontal bone loss was 11.0 (SD 4.5) % among healthy to mild periodontitis patients (stages 0–1), 25.3 (SD 12.1) % for non-treated periodontitis (stages 2–4) and 27.3 (SD 11.6) % for treated stage 2–4 periodontitis subjects, respectively (Supp. Tables 3 & 4). Subjects with treated stage 2–4 periodontitis presented similar confounders to those with non-treated periodontitis (stages 2–4), except for cardiovascular diseases, hypertension and diabetes that were significantly more common in non-treated periodontitis ( $p < 0.05$ ) (Table 2).

The presence of periodontitis (stages 2–4) (regardless of treatment) was associated with age, BMI, sex, citizenship status, smoking habits, hypertension, diabetes, cardiovascular diseases, COPD, peptic ulcer, cancer, chronic kidney disease and organ transplantation (Table 2). The following comorbidities were significantly more common in non-treated periodontitis group than in treated periodontitis: cancer, kidney disease, organ transplant, cardiovascular disease, diabetes, hypertension and non-citizens ( $p < 0.05$ ; Fisher's exact test).

Risk analysis of COVID-19 complications revealed that while periodontitis stage 2–4 (regardless of treatment) was

associated with higher risk of complications (i.e. need for mechanical ventilation [AOR = 3.32, 95% CI 1.10–10.08,  $p = 0.034$ ]) (Supp. Table 1), subjects with treated periodontitis had a lower risk than the non-treated ones. Adjusted OR analysis comparing treated and non-treated periodontitis (stages 2–4) revealed that treated patients were at lower risk of complications; however, this was not statistically significant (Supp. Table 2). On the other hand, adjusted OR analysis comparing periodontitis patients to healthy ones showed that non-treated periodontitis was associated with a significant risk of need for mechanical ventilation (AOR = 3.91; 95% CI 1.21–12.57,  $p = 0.034$ , while for treated periodontitis, the risk was not significant (AOR = 1.28; 95% CI 0.25–6.58,  $p = 0.768$ ) (Table 3).

Figures 1 and 2 depict the blood biomarkers analyses comparing periodontally healthy (stage 0–1 periodontitis), non-treated periodontitis (stages 2–4), and treated periodontitis stages 2–4 subjects at admission and discharge, respectively. Compared to periodontally healthy patients, periodontitis stage 2–4 patients (both treated and non-treated) had significantly higher levels of creatine, urea, and HbA1c, throughout the course of their COVID-19 disease as well as higher levels of ferritin, vitamin D, and CRP at the initial stage of COVID-19. Compared to periodontally healthy patients, non-treated periodontitis (stage 2–4) subjects showed significantly lower levels of lymphocytes upon admission and higher levels of D-dimer, CRP and ferritin before discharge.

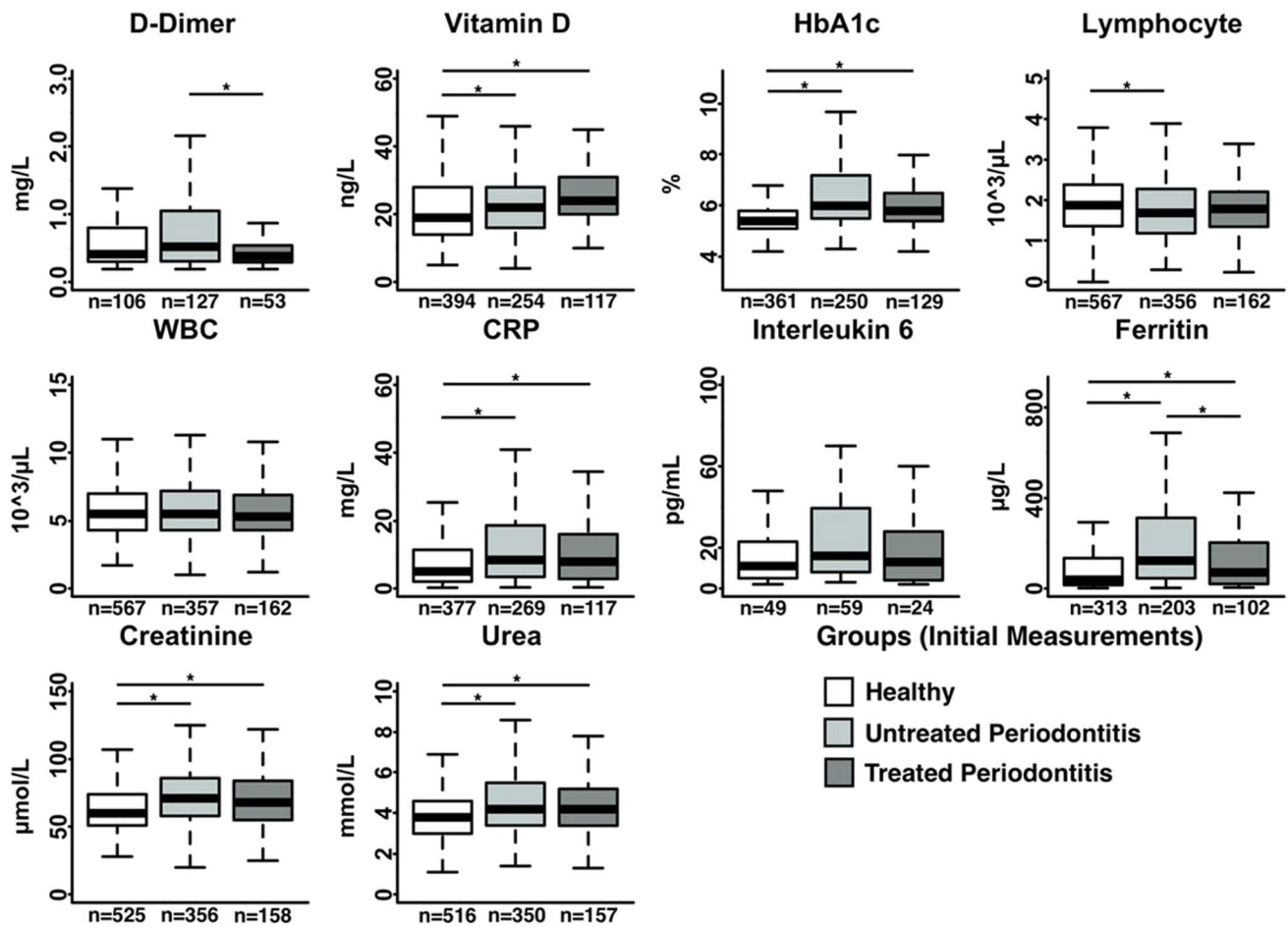
Furthermore, subjects with treated periodontitis (stages 2–4) demonstrated significantly lower levels of D-dimer and ferritin compared to non-treated periodontitis patients

**Table 3** Risk analysis of COVID-19 complications (any complication, ICU admission, ventilation and death) associated with treated periodontitis and untreated periodontitis

| Periodontal condition     | COVID-19 complications |             | OR (95% CI)       | AOR (95% CI)*            | Adjusted p   |
|---------------------------|------------------------|-------------|-------------------|--------------------------|--------------|
|                           | None                   | Any         |                   |                          |              |
| No periodontitis          | 698                    | 23          | 1                 | 1                        |              |
| Non-treated periodontitis | 375                    | 42          | 3.40 (2.01–5.74)  | 1.92 (0.96–3.83)         | 0.065        |
| Treated periodontitis     | 181                    | 6           | 1.01 (0.40–2.51)  | 1.39 (0.48–4.04)         | 0.543        |
|                           | None                   | Ventilation |                   |                          |              |
| No periodontitis          | 698                    | 6           | 1                 | 1                        |              |
| Non-treated periodontitis | 375                    | 23          | 7.14 (2.88–17.68) | <b>3.91 (1.21–12.57)</b> | <b>0.022</b> |
| Treated periodontitis     | 181                    | 3           | 1.93 (0.48–7.78)  | 1.28 (0.25–6.58)         | 0.768        |
|                           | None                   | Deceased    |                   |                          |              |
| No periodontitis          | 698                    | 5           | 1                 | 1                        |              |
| Non-treated periodontitis | 375                    | 13          | 4.84 (1.71–13.68) | 3.56 (0.55–22.73)        | 0.181        |
| Treated periodontitis     | 181                    | 1           | 0.77 (0.09–6.64)  | 1.13 (0.07–18.43)        | 0.993        |
|                           | None                   | ICU         |                   |                          |              |
| No periodontitis          | 698                    | 21          | 1                 | 1                        |              |
| Non-treated periodontitis | 375                    | 35          | 3.10 (1.78–5.41)  | 1.81 (0.88–3.69)         | 0.104        |
| Treated periodontitis     | 181                    | 6           | 1.10 (0.44–2.77)  | 1.31 (0.45–3.81)         | 0.618        |

\*Adjusted to sex, age, diabetes, smoking habits, BMI and co-morbidities





**Fig. 1** Box plots of the blood work of COVID-19 patients at admission (initial) comparing patients without periodontitis with those with periodontitis that have received treatment for periodontitis and those

that did not receive periodontal treatment. (\*) indicates significant differences between groups ( $p < 0.05$ ). The letter n indicates the number of patients analysed for each parameter and condition

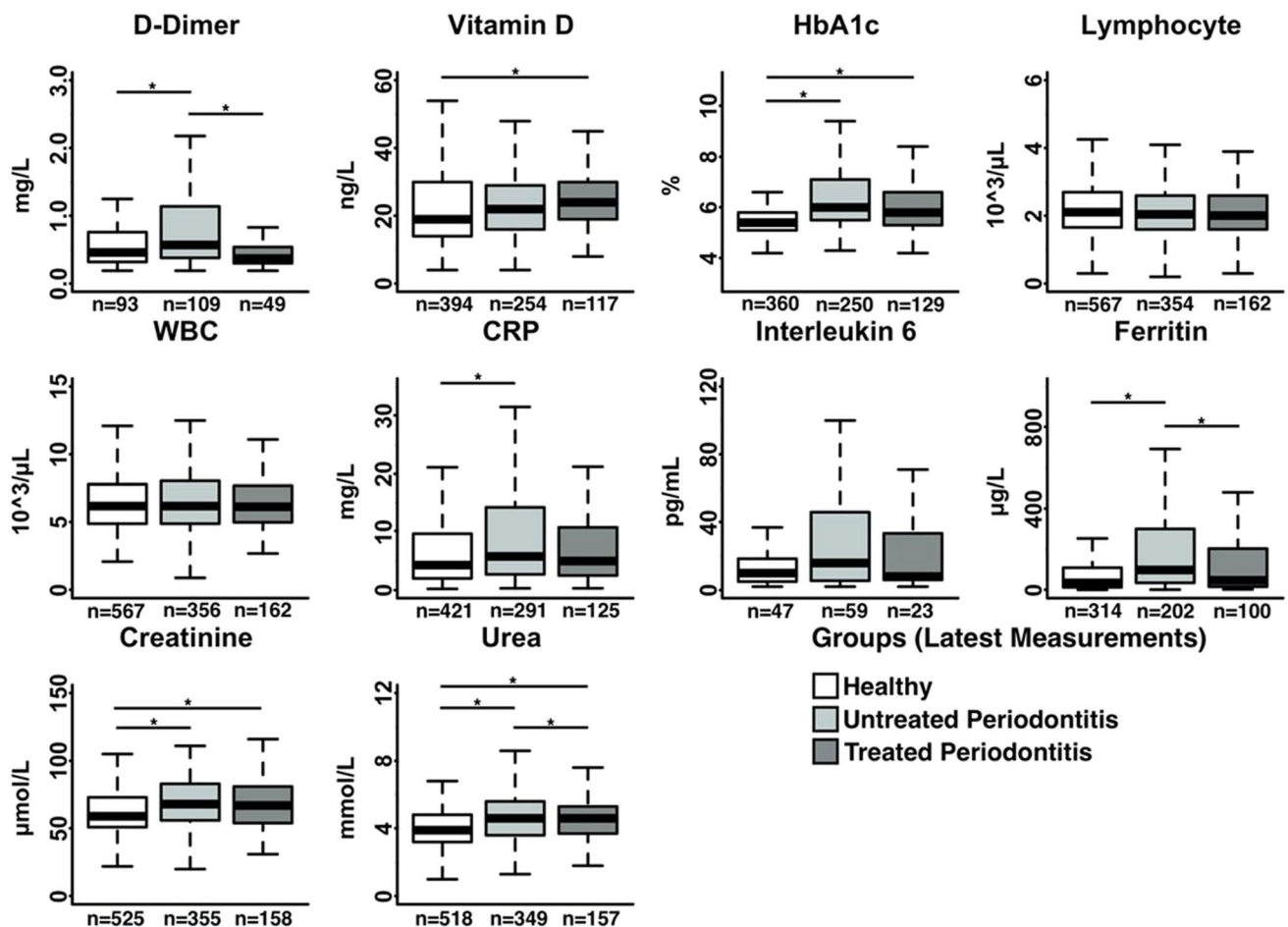
throughout the course of their COVID-19 disease, and lower levels of urea at the later stage of the disease. Other biomarkers such as HbA1c, and IL-6 showed higher levels in non-treated periodontitis when compared to treated subjects, but these differences were not significant.

Among the 110 patients that underwent bacterial culture from respiratory sites, only 9 had positive cultures, 5 of whom were also periodontitis subjects. However, there was no significant association between the periodontitis and positive bacterial cultures (OR = 0.79 95% CI 0.20–3.11;  $p = 0.731$ ). The bacterial species identified were *Stenotrophomonas maltophilia*, *Staphylococcus hominis*, *Staphylococcus epidermidis*, *Pseudomonas putida* and *Klebsiella pneumoniae*. Cases with positive cultures for *Stenotrophomonas maltophilia* ( $n = 2$ ) and *Staphylococcus hominis* ( $n = 1$ ) corresponded to patients without periodontitis; *Staphylococcus epidermidis* ( $n = 3$ ) and *Klebsiella pneumoniae* ( $n = 1$ ) were only found in patients with non-treated periodontitis and *Pseudomonas putida* ( $n = 1$ ) in a patient

with treated periodontitis. Among these 9 patients with bacterial pulmonary infections, 7 were admitted to the ICU, 6 needed mechanical ventilation, and 4 died.

## Discussion

This study revealed that, compared to periodontally healthy patients, patients with moderate to advanced periodontitis (stages 2–4) who did not receive periodontal therapy could be at higher risk of needing mechanical ventilation. On the other hand, periodontitis patients that received periodontal care were not associated with increased risk of COVID-19 complications. Diagnosis of periodontitis (stages 2–4) was associated with increased levels of serum biomarkers of inflammation, coagulation, diabetes and kidney dysfunction even among treated patients. However, compared to non-treated periodontitis subjects, treated periodontitis patients had significantly



**Fig. 2** Box plots of the blood work of COVID-19 patients before being discharged, comparing patients without periodontitis with those with periodontitis that have received treatment for periodontitis and

those that did not receive periodontal treatment. (\*) indicates significant differences between groups ( $p < 0.05$ ). The letter n indicates the number of patients analysed for each parameter and condition

lower levels of D-dimer and ferritin throughout the course of the disease and lower levels of urea prior to discharge.

The significant association between non-treated periodontitis and mechanical ventilation corroborates previous reports linking periodontitis to COVID-19 complications. A previous study demonstrated a significant association between periodontitis and the need for mechanical ventilation (AOR = 4.57, 95% CI 1.19–17.4) [11], and other studies based on phone surveys found an association between periodontitis and COVID-19-related hospital admissions and mortality [22]. However, this study presents evidence on the possible impact of periodontal therapy on COVID-19 complications, adding more evidence to the already known effect of periodontal therapy on systemic conditions such as diabetes and cardiovascular diseases [23].

Periodontitis and severe COVID-19 share several common risk factors such as age, obesity, diabetes and hypertension, among others [23–25]. Therefore, it may be argued that these predisposing conditions could be behind the

association between periodontitis and unfavourable COVID-19 outcomes. However, the findings of this study strengthen the hypothesis linking COVID-19 complications directly to periodontitis.

In this study, patients with non-treated moderate-to-advanced periodontitis (stages 2–4) presented higher risk of COVID-19-related ICU admissions and death; however, these associations were not significant. This contradicts previous findings demonstrating a significant association of periodontitis with COVID-19-related deaths (AOR = 8.81, 95% CI 1.00–77.7) and ICU admissions (AOR = 3.54, 95% CI 1.39–9.05) [11]. This could be explained by the changes in the lethality of virus variants across the course of the pandemic. While our first study was limited to the first and deadliest COVID-19 wave in Qatar, the present study covers an extended observational period of the pandemic that includes a second phase of the pandemic that was characterized by lower lethality [26]. Accordingly, the proportionally smaller number of deaths in this second study limited our ability



to analyse the risk of death associated with periodontitis. This observation also implies that the nature of the SARS-CoV2 variants and COVID-19 waves could indeed play a role in the association between periodontitis and COVID-19 severity.

Sub-analysis of COVID-19 complications in our study was necessary because COVID-19 deaths are uncommon and ICU admission may depend on physicians' subjective evaluations [27, 28]. This is particularly relevant in the context of Qatar because due to its young population and well-functioning healthcare system it had one of the lowest rates of COVID-19 complication in the world [28]. This implies that in other populations with higher rates of COVID-19 complications, periodontal health might have a different impact.

In this study, regardless of periodontal therapy, patients with periodontitis presented higher blood levels of inflammatory biomarkers than those without periodontitis. This corroborates different investigations showing that periodontitis is associated with systemic inflammation biomarkers such as CRP, IL-1 and IL-6 [23, 29, 30]. Since COVID-19 complications are associated with the same biomarkers [31], it has been hypothesized that periodontitis could influence COVID-19 outcomes through its impact on systemic inflammation by priming the immune system to an exacerbated reaction to COVID-19 [32]. It has also been proposed that viral infections could play a role in the association between periodontitis and systemic conditions through their ability to exacerbate inflammation, compromise the immune responses and synergize with bacteria [33]. For instance, viruses from the herpes and human papillomavirus families cause primary viral infections in the oral cavity, and two herpesviruses, Epstein-Barr virus and cytomegalovirus, have been associated with marginal periodontitis and the inflammatory process of periapical bone destruction [34, 35].

Interestingly, in the current study, ferritin, an indicator of systemic inflammation, presented lower serum levels in patients with treated periodontitis compared to non-treated periodontitis. A similar observation was made on the levels of CRP before patient discharge. This could confirm that the impact of periodontitis and periodontal care on COVID-19 complications could be mediated by inflammatory pathways.

D-dimer, a coagulation biomarker indicative of thrombosis, presented significantly lower levels in treated than in non-treated periodontitis patients. This seems to suggest that coagulopathy may also be linking COVID-19 complications with periodontitis and that periodontitis could be exacerbating COVID-19 coagulopathies as hypothesized by Lloyd-Jones et al. [36], although further research would be needed to confirm this.

Periodontitis has a well-established association with coagulopathies. Periodontitis has been associated with platelet activation [37], and periodontal care has been shown to

improve endothelial function and coagulation disorders [38] and reduce the levels of D-dimer [39]. On the other hand, D-dimer levels are known to increase in COVID-19 patients, as a reflection of coagulation activation caused by viremia, inflammation, superinfection and/or organ dysfunction, and they are directly correlated to COVID-19 complications and mortality [40].

Another possible mechanism linking periodontitis with COVID-19 severity may be the well-established association between oral health and respiratory diseases [41–43]. The oral cavity is a reservoir for respiratory pathogens [43, 44], and periodontitis and poor oral hygiene have been associated with increased risk of pneumonia [45], while periodontal care has been shown to prevent deaths from pneumonia in high-risk patients [46]. Thus, it has been hypothesized that periodontitis could aggravate COVID-19 by increasing the risk of direct oral bacteria aspiration or inoculation into the lower respiratory tract [41, 47]. In this study, out of the 110 patients that underwent lung swaps, only nine presented positive bacterial cultures, and among them, only five had signs of periodontitis, indicating no significant association between periodontitis and the risk of pulmonary bacterial infections among this group of COVID-19 patients. The limited number of patients with microbial testing from respiratory sites prevented us from drawing clear conclusions on the links between periodontal microbes and secondary lung infections in COVID-19 patients. Nevertheless, the bacteria species identified (*Stenotrophomonas maltophilia*, and *Staphylococcus hominis*, *Staphylococcus epidermidis*, *Pseudomonas putida* and *Klebsiella pneumoniae*) are all known to be present in the oral cavity [48–54]. In this study, *Stenotrophomonas maltophilia*, an antibiotic resistant opportunistic bacteria found in the oral cavity of immunocompromised patients [53, 54], was only identified in patients without periodontitis. Similarly, *Staphylococcus hominis* was only found in patients without periodontitis, although this bacterium could be found in periodontitis and periapical lesions [51, 52]. In contrast, *Staphylococcus epidermidis* ( $n = 3$ ), *Pseudomonas putida* ( $n = 1$ ) and *Klebsiella pneumoniae* ( $n = 1$ ) were only found in patients with periodontitis. *Staphylococcus epidermidis* are found in the oral cavity, especially in patients with periodontitis [51], and *Klebsiella pneumoniae* are found in periodontal pockets [50]. The small incidence of bacterial infections reported in this study seems to indicate that aspiration of periodontal pathogens to the lung probably plays a minor role in the association between periodontitis and COVID-19 complications. However, even though these numbers were small, the mortality associated with these cases was extremely high (4 out of the 9 patients with positive cultures died), amounting to 21% of all registered fatalities.

The national COVID-19 protocols implemented during the study period included the prophylactic administration of azithromycin for hospitalized COVID-19 patients. As a result of this policy, almost 80% of the patients hospitalized in our study received azithromycin. This antibiotic is known to have beneficial effects against periodontitis [55], and thus it could be hypothesized that periodontitis patients would have benefited from it. However, future studies would be needed to investigate this possibility.

One of the limitations of this observational study is that the periodontal clinical examination of COVID-19 patients was not feasible, and the use of radiographs and dental records was the best available option for assessing periodontal status and effectiveness of periodontal treatments prior to COVID-19 infection. Nonetheless, previous studies have shown that radiological bone loss is a good indicator for periodontitis [56], and we were able to validate our assessments using the subset of patients registered at the Division of Periodontics at HMC.

Various socioeconomic factors such as education, income and willingness to contact medical and dental providers could also be confounders that might have an impact on oral diseases and COVID-19 severity. In our study, we were not able to obtain direct information on these parameters, and this is a limitation. However, we were able to analyse and adjust for an indirect socioeconomic indicator, which is the citizenship status, a strong indicator of household income in Qatar. A similar approach has been used in previous COVID-19 studies in Qatar [57]. Our analyses showed that Qatari citizens had lower incidence of periodontitis and higher rates of periodontal treatment, probably due to their access to preventive dental care programs. However, citizenship was not independently associated with higher risk of COVID-19 complications, probably because the non-citizenship segment of the population is relatively young in age, and all COVID-19 patients received free access to medical care.

Another limitation was that periodontal therapy was not randomized; hence, differences between treated and non-treated groups might not be solely attributed to the interventions but could also result from other unaccounted factors. Indeed, periodontal therapy was significantly associated with some confounders (Table 2), although our statistical analysis adjusted for this.

This study was conducted on non-vaccinated subjects and the data was collected before COVID-19 vaccines became available to the subjects; thus, the associations observed might be different in vaccinated patients.

Despite these limitations, the reported findings have important clinical implications. The fact that patients with treated periodontitis were less likely to suffer COVID-19 complications than non-treated ones further strengthens the hypothesis linking periodontitis to COVID-19

complications and suggests that managing periodontitis could help reduce the risk for COVID-19 complications, although future research is needed to verify this.

In conclusion, this observational study showed that COVID-19 patients with non-treated periodontitis (stages 2–4) were significantly more likely to need mechanical ventilation; however, this risk was not significant for patients with treated periodontitis. Increased blood levels of D-dimer and ferritin in patients with non-treated periodontitis compared to periodontally healthy and treated periodontitis patients could imply that periodontitis increases the risk of COVID-19 complications through its detrimental effects on inflammation and coagulation.

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

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## Declarations

**Ethics 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-01–20-1228.

**Consent to participate** Informed consent was waived under the pandemic response framework of Institutional Review Board of Hamad Medical Corporation.

**Conflict of interest** The authors declare no competing interests.

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## References

- Greenberg N, Docherty M, Gnanapragasam S, Wessely S (2020) Managing mental health challenges faced by healthcare workers during COVID-19 pandemic. *BMJ* 368:m1211
- Zhang D, Hu M, Ji Q (2020) Financial markets under the global pandemic of COVID-19. *Financ Res Lett* 36:101528
- Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC (2020) Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): A Review. *JAMA* 324(8):782–793
- Iacobucci G (2021) Covid-19: New UK variant may be linked to increased death rate, early data indicate. *BMJ* 372:n230
- Bohn MK, Hall A, Sepiashvili L, Jung B, Steele S, Adeli K (2020) Pathophysiology of COVID-19: mechanisms underlying disease severity and progression. *Physiology (Bethesda)* 35(5):288–301
- Shi W, Lv J, Lin L (2020) Coagulopathy in COVID-19: focus on vascular thrombotic events. *J Mol Cell Cardiol* 146:32–40
- Ye Q, Wang B, Mao J (2020) The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. *J Infect* 80(6):607–613. <https://doi.org/10.1016/j.jinf.2020.03.037>
- Hatmi ZN (2021) A systematic review of systematic reviews on the COVID-19 pandemic. *SN Compr Clin Med* 3(2):419–436. <https://doi.org/10.1007/s42399-021-00749-y>
- Genco RJ, Sanz M (2020) Clinical and public health implications of periodontal and systemic diseases: an overview. *Periodontol* 2000 83(1):7–13
- Elisetti N (2021) Periodontal pocket and COVID-19: could there be a possible link? *Med Hypotheses* 146:110355. <https://doi.org/10.1016/j.mehy.2020.110355>
- Marouf N, Cai W, Said KN, Daas H, Diab H, Chinta VR et al (2021) Association between periodontitis and severity of COVID-19 infection: a case-control study. *J Clin Periodontol* 48(4):483–491
- Kamel AHM, Basuoni A, Salem ZA, AbuBakr N (2021) The impact of oral health status on COVID-19 severity, recovery period and C-reactive protein values. *Br Dent J* 1–7. <https://doi.org/10.1038/s41415-021-2656-1>
- Sirin DA, Ozcelik F (2021) The relationship between COVID-19 and the dental damage stage determined by radiological examination. *Oral Radiol* 37(4):600–609
- Larvin H, Wilmott S, Kang J, Aggarwal VR, Pavitt S, Wu J (2021) Additive effect of periodontal disease and obesity on COVID-19 outcomes. *J Dent Res* 100(11):1228–1235
- Genco RJ, Graziani F, Hasturk H (2020) Effects of periodontal disease on glycemic control, complications, and incidence of diabetes mellitus. *Periodontol* 2000 83(1):59–65
- Orlandi M, Graziani F, D'Aiuto F (2020) Periodontal therapy and cardiovascular risk. *Periodontol* 2000 83(1):107–24
- Park SY, Kim SH, Kang SH, Yoon CH, Lee HJ, Yun PY et al (2019) Improved oral hygiene care attenuates the cardiovascular risk of oral health disease: a population-based study from Korea. *Eur Heart J* 40(14):1138–1145
- Papapanou PN, Sanz M, Buduneli N, Dietrich T, Feres M, Fine DH et al (2018) Periodontitis: consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *J Periodontol* 89(Suppl 1):S173–S182
- Hellen-Halme K, Lith A, Shi XQ (2020) Reliability of marginal bone level measurements on digital panoramic and digital intraoral radiographs. *Oral Radiol* 36(2):135–140
- Tonetti MS, Greenwell H, Kornman KS (2018) Staging and grading of periodontitis: framework and proposal of a new classification and case definition. *J Clin Periodontol* 45(Suppl 20):S149–S161
- Schneeweiss S, Maclure M (2000) Use of comorbidity scores for control of confounding in studies using administrative databases. *Int J Epidemiol* 29(5):891–898
- Larvin H, Wilmott S, Wu J, Kang J (2020) The impact of periodontal disease on hospital admission and mortality during COVID-19 pandemic. *Front Med (Lausanne)* 7:604980
- Sanz M, Marco Del Castillo A, Jepsen S, Gonzalez-Juanatey JR, D'Aiuto F, Boucharad P et al (2020) Periodontitis and cardiovascular diseases: consensus report. *J Clin Periodontol* 47(3):268–288
- Billings M, Holtfreter B, Papapanou PN, Mitnik GL, Kocher T, Dye BA (2018) Age-dependent distribution of periodontitis in two countries: findings from NHANES 2009 to 2014 and SHIP-TREND 2008 to 2012. *J Periodontol* 89(Suppl 1):S140–S158
- Liu H, Chen S, Liu M, Nie H, Lu H (2020) Comorbid chronic diseases are strongly correlated with disease severity among COVID-19 patients: a systematic review and meta-analysis. *Aging Dis* 11(3):668–678
- Abu-Raddad LJ, Chemaitelly H, Bertollini R, National study group for COVID-19 epidemiology (2021) Severity of SARS-CoV-2 Reinfections as Compared with Primary Infections. *N Engl J Med* 23(26):2487–2489
- Grasselli G, Cattaneo E, Florio G, Ippolito M, Zanella A, Cortegiani A et al (2021) Mechanical ventilation parameters in critically ill COVID-19 patients: a scoping review. *Crit Care* 25(1):115
- Omran AS, Almaslamani MA, Daghfal J, Alattar RA, Elgara M, Shaar SH et al (2020) The first consecutive 5000 patients with coronavirus disease 2019 from Qatar; a nation-wide cohort study. *BMC Infect Dis* 20(1):777
- Tonetti MS, Jepsen S, Jin L, Otomo-Corgel J (2017) Impact of the global burden of periodontal diseases on health, nutrition and wellbeing of mankind: a call for global action. *J Clin Periodontol* 44(5):456–462
- Hajishengallis G (2022) Interconnection of periodontal disease and comorbidities: evidence, mechanisms, and implications. *Periodontol* 2000 89(1):9–18
- Mulchandani R, Lyngdoh T, Kakkar AK (2021) Deciphering the COVID-19 cytokine storm: systematic review and meta-analysis. *Eur J Clin Invest* 51(1):e13429
- Tamimi F, Altigani S, Sanz M (2022) Periodontitis and coronavirus disease 2019. *Periodontol* 2000 89(1):207–214
- Teles F, Collman RG, Mominkhan D, Wang Y (2022) Viruses, periodontitis, and comorbidities. *Periodontol* 2000 89(1):190–206
- Martínez A, Kuraji R, Kapila YL (2021) The human oral virome: shedding light on the dark matter. *Periodontol* 2000 87(1):282–298
- Naqvi AR, Slots J (2021) Human and herpesvirus microRNAs in periodontal disease. *Periodontol* 2000 87(1):325–339
- Lloyd-Jones G, Molayem S, Pontes C, Chapple I (2021) The COVID-19 pathway: a proposed oral-vascular-pulmonary route of SARS-CoV-2 infection and the importance of oral healthcare measures. *Genesis-JOMDR* 2:1–25
- Papapanagiotou D, Nicu EA, Bizzarro S, Gerdes VE, Meijers JC, Nieuwland R et al (2009) Periodontitis is associated with platelet activation. *Atherosclerosis* 202(2):605–611
- Tonetti MS, D'Aiuto F, Nibali L, Donald A, Storry C, Parkar M, Suvan J, Hingorani AD, Vallance P, Deanfield J (2007) Treatment of periodontitis and endothelial function. *N Engl J Med* 356(9):911–920

39. D’Aiuto F, Paskar M, Tonetti MS (2007) Acute effects of periodontal therapy on bio-markers of vascular health. *J Clin Periodontol* 34(2):124–129
40. Wool GD, Miller JL (2021) The Impact of COVID-19 disease on platelets and coagulation. *Pathobiology* 88(1):15–27
41. Aquino-Martinez R, Hernández-Vigueras S (2021) Severe COVID-19 lung infection in older people and periodontitis. *J Clin Med* 10(2):279. <https://doi.org/10.3390/jcm10020279>
42. Awano S, Ansai T, Takata Y, Soh I, Akifusa S, Hamasaki T, Yoshida A, Sonoki K, Fujisawa K, Takehara T (2008) Oral health and mortality risk from pneumonia in the elderly. *J Dent Res* 87(4):334–339
43. Takahashi Y, Watanabe N, Kamio N, Kobayashi R, Iinuma T, Imai K (2020) Aspiration of periodontopathic bacteria due to poor oral hygiene potentially contributes to the aggravation of COVID-19. *J Oral Sci* 63(1):1–3. <https://doi.org/10.2334/josnusd.20-0388>
44. Bao L, Zhang C, Dong J, Zhao L, Li Y, Sun J (2020) Oral microbiome and SARS-CoV-2: beware of lung co-infection. *Front Microbiol* 11:1840
45. Scannapieco FA, Ho AW (2001) Potential associations between chronic respiratory disease and periodontal disease: analysis of National Health and Nutrition Examination Survey III. *J Periodontol* 72(1):50–56
46. Yang LC, Suen YJ, Wang YH, Lin TC, Yu HC, Chang YC (2020) The association of periodontal treatment and decreased pneumonia: a nationwide population-based cohort study. *Int J Environ Res Public Health* 17(1):356. <https://doi.org/10.3390/ijerph17010356>
47. Sampson V, Kamona N, Sampson A (2020) Could there be a link between oral hygiene and the severity of SARS-CoV-2 infections? *Br Dent J* 228(12):971–975
48. Bergamo AZN, de Oliveira KMH, Matsumoto MAN, Nascimento CD, Romano FL, da Silva RAB et al (2019) Orthodontic appliances did not increase risk of dental caries and periodontal disease under preventive protocol. *Angle Orthod* 89(1):25–32
49. Chan XY, Chua KO, How KY, Yin WF, Chan KG (2014) Global genome comparative analysis reveals insights of resistome and life-style adaptation of *Pseudomonas putida* strain T2-2 in oral cavity. *Sci World J* 2014:930727. <https://doi.org/10.1155/2014/930727>
50. Goncalves MO, Coutinho-Filho WP, Pimenta FP, Pereira GA, Pereira JA, Mattos-Guaraldi AL et al (2007) Periodontal disease as reservoir for multi-resistant and hydrolytic enterobacterial species. *Lett Appl Microbiol* 44(5):488–494
51. Murdoch FE, Sammons RL, Chapple IL (2004) Isolation and characterization of subgingival staphylococci from periodontitis patients and controls. *Oral Dis* 10(3):155–162
52. Narita M, Shibahara T, Takano N, Fujii R, Okuda K, Ishihara K (2016) Antimicrobial susceptibility of microorganisms isolated from periapical periodontitis lesions. *Bull Tokyo Dent Coll* 57(3):133–142
53. Prates M, Fernandes F, Proença F, Mussa Y, Tavares A, Pereira A (2020) Oral infection caused by *Stenotrophomonas maltophilia*: a rare presentation of an emerging opportunistic pathogen. *Case Rep Infect Dis* 2020:6346120
54. Soga Y, Saito T, Nishimura F, Ishimaru F, Mineshiba J, Mineshiba F et al (2008) Appearance of multidrug-resistant opportunistic bacteria on the gingiva during leukemia treatment. *J Periodontol* 79(1):181–186
55. Zhang Z, Zheng Y, Bian X (2016) Clinical effect of azithromycin as an adjunct to non-surgical treatment of chronic periodontitis: a meta-analysis of randomized controlled clinical trials. *J Periodontol Res* 51(3):275–283
56. Machado V, Proença L, Morgado M, Mendes JJ, Botelho J (2020) Accuracy of panoramic radiograph for diagnosing periodontitis comparing to clinical examination. *J Clin Med* 9(7):2313. <https://doi.org/10.3390/jcm9072313>
57. Chemaitelly H, Tang P, Hasan MR, AlMukdad S, Yassine HM, Benslimane FM, Al Khatib HA, Coyle P, Ayoub HH, Al Kanaani Z, Al Kuwari E, Jeremijenko A, Kaleeckal AH, Latif AN, Shaik RM, Abdul Rahim HF, Nasrallah GK, Al Kuwari MG, Al Romaihi HE, Butt AA, Al-Thani MH, Al Khal A, Bertollini R, Abu-Raddad LJ (2021) Waning of BNT162b2 vaccine protection against SARS-CoV-2 infection in Qatar. *N Engl J Med* 385(24):e83

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