Review

The Bidirectional Association Between Periodontitis and COVID-19: A Review of Current Evidence

Miriam Ting *, Rodrigo Neiva, Leenus Tafline, Jon B Suzuki

Posted Date: 23 May 2023

doi: 10.20944/preprints202305.1601.v1

Keywords: COVID-19; SARS-CoV-2; Periodontitis; Herpesviruses; Periodontal; Biomarkers

Review

The Bidirectional Association between Periodontitis and COVID-19: A Review of Current Evidence

Miriam Ting [1,2,*], Rodrigo Neiva [1], Leenus Tafline [2] and Jon Suzuki [3,4,5,6,7]

[1] Department of Periodontics, School of Dental Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA
[2] Think Dental Learning Institute Paoli, PA 19301, USA
[3] Department of Graduate Periodontics, University of Maryland, Baltimore, MD 20742, USA
[4] Department of Graduate Prosthodontics, University of Washington, Seattle, WA 98195, USA
[5] Department of Graduate Periodontics, Nova Southeastern University, Fort Lauderdale, FL 33314, USA
[6] Department of Microbiology and Immunology (Medicine), Temple University, Philadelphia, PA 19140, USA
[7] Department of Periodontology and Oral Implantology (Dentistry), Temple University, Philadelphia, PA 19140, USA
* Correspondence: Thinkdentallearninginstitute@gmail.com

Abstract: The COVID-19 pandemic has brought marked changes worldwide to the management of airborne infectious diseases. It sparked the development of the SARS-CoV-2 vaccine and pharmacotherapeutics to prevent infection and increase the survival rate during the acute viral phase and the comorbidities associated with COVID-19. Periodontal disease may increase the morbidity and perhaps the mortality of a COVID-19 infection. However, the molecular interaction between periodontitis and COVID-19 infection remains undetermined. A potential pathogenic co-morbidity may involve periodontal pathogenic release of destructive cytokines in the highly inflamed connective tissue and risk for COVID-19. Additional biomarkers such as C-reactive proteins appear to play a role for risk and pathogenesis of COVID-19. The potential of herpesviruses, especially as it is related to aggressive periodontitis may also be a comorbidity for COVID-19. This paper reviews available evidence on the bidirectional association between periodontitis and COVID-19.

Keywords: COVID-19; SARS-CoV-2; periodontitis; herpesviruses; periodontal; biomarkers

1. Introduction

On March 11, 2020, the World Health Organization declared a global coronavirus disease of 2019 (COVID-19) pandemic [1]. The COVID-19 pandemic is caused by the newly discovered severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). When an infected individual speaks, sneezes, coughs, sings, or breathes; SARS-CoV-2 can spread from their mouth or nose via microscopic droplet particles. COVID-19 complications are more likely in older individuals and those with underlying medical disorders like cancers, diabetes, cardiovascular diseases, or chronic respiratory diseases [2–4]. These comorbidities are also associated with periodontitis [5–9].

According to the American Dental Association, periodontitis is an inflammatory disease of bacterial etiology resulting in the loss of periodontal tissue attachment and alveolar bone [10]. It is among the most widespread conditions affecting the oral cavity and continues to be a worldwide health concern. Periodontal disease must be treated quickly since it may impact the patient's general health [11].

The potential pathway for the relationship between periodontal health and systemic health includes periodontitis associated putative pathogenic oral microbiota, overexpression of local and systemic pro-inflammatory destructive cytokine [12,13]. In addition, the reactivation of latent systemic herpesvirus infections has been associated with the onset of aggressive periodontal disease [14]. Active human cytomegalovirus infection has been detected in deep periodontal pockets in

 doi:10.20944/preprints202305.1601.v1

localized aggressive periodontitis patients [15]. Therefore, at least several viruses have recently been implicated in potentiating periodontal infections. It is plausible that this herpetic viral coinfection may have an additive effect on COVID-19 risk.

Research has shown that SARS-CoV-2 enters the body through ACE-2 receptors on the surface of host cells. ACE-2 receptor expression related to systemic conditions like hypertension, chronic obstructive pulmonary disease (COPD), hepatic disorders, renal dysfunctions or diabetes, can facilitate viral entrance into host cells [16]. The primary function of the angiotensin-converting enzyme (ACE) in the renin-angiotensin system (RAS) is to inhibit the levels of angiotensin II and raise the levels of angiotensin I-7, this activates molecular signaling pathways associated with tissue damage and inflammation [17].

Studies have shown that ACE-2 receptors in human pulmonary epithelial cells are upregulated by periodontopathic bacteria [18]. Additionally, the ACE-2 receptors found on periodontal tissue cells allow the virus to enter and circulate throughout the body. When compared to the lungs, the oral cavity expresses many ACE-2 receptors [19–21]. SARS-CoV-2 found in dental biofilm and periodontal tissues showed that the periodontal and oral environments may contribute to COVID-19 infectivity [22]. Additionally, the blocking of SARS-CoV-2 invasion via the blocking the ACE-2 receptors and decreasing transmembrane serine protease 2 (TMPRSS2), may also prevent SARS-CoV-2 infection of the periodontal epithelium [23].

2. Effect of periodontitis on SARS-CoV-2 entry molecules

For a person to be vulnerable to the SARS-CoV-2, the virus must first successfully enter the host cells. There are multiple pathways by which SARS-CoV-2 can enter human cells [24]. These pathways involve the virus targeting these SARS-CoV-2 entry molecules present on the host cells. These molecules include ACE-2 receptors, TMPRSS2, and furin. These SARS-CoV-2 entry molecules promote virus entry into the host cells and are determinants of COVID-19 infection [25,26].

SARS-CoV-2 entry molecules are present on the dorsal tongue and gingiva. Saliva and tongue coatings were sampled to determine the presence of these molecules in the oral cavity. Immunohistochemical studies detected ACE-2 receptors in the stratified squamous epithelium of the dorsal tongue and gingiva. The ACE-2-positive cells were 2.2% of the oral tissue, of which 92% were epithelial cells [27]. Similarly, TMPRSS2 was found in the stratified squamous epithelium of the gingival keratinized surface layer. TMPRSS2 was also detected in saliva and tongue coatings via Western blot. Furin was localized mainly in the lower layers of the stratified squamous epithelium. Furin was detected in the saliva but not in tongue-coating samples [25,26]. ACE-2, TMPRSS2, and furin mRNA expression were present in taste bud-derived cultured cells, and this was further supported by immunofluorescence observations [27].

The periodontal pocket epithelium may be an entry point for SARS-CoV-2, because it expresses both ACE-2 receptors and TMPRSS2. In addition, the pocket epithelium cell layer may be thin and exhibit microulcerations; thus, increasing the risk of SARS-CoV-2 entry and infection [28].

Other factors such as salivary levels of ACE-2 were found to increase with the severity of the periodontitis and were positively associated with the alveolar bone loss [29].

ACE-2 receptors were identified in 2003 as the entry receptor for SARS-CoV. SARS-CoV-2 shares 79.5% genome sequence identity with SARS-CoV [30]. Thus, SARS-CoV-2 and SARS-CoV can enter the host cell via the same receptor. Organ dysfunction caused by SARS-CoV-2, such as acute respiratory distress syndrome (ARDS), acute cardiac injury, acute kidney injury, and acute hepatic injury, is common in severe cases. However, the overall mortality rate of COVID-19 caused by SARS-CoV-2 was lower than SARS and MERS [30].

SARS-CoV-2 entry into cells is particular to ACE-2 expressing cells; other coronavirus receptors like aminopeptidase N and dipeptidyl peptidase (DPP4) do not have the same effect [30]. The binding affinity of the SARS-CoV-2 spike glycoprotein to the ACE-2 receptor is 10–20 fold higher than that of SARS-CoV [31,32]. The ACE-2 receptor in the host cell membrane and furin cleavage site of SARS-CoV-2 allowed the virus to invade the host cells [33–35]. ACE-2 and TMPRSS2 are also expressed in

 doi:10.20944/preprints202305.1601.v1

various organs throughout the body, including the lung, heart, pancreas, kidney, bladder, small intestine, and skin [25,26].

TMPRSS2 is another essential factor that facilitates SARS-COV-2 entry and infectivity. TMPRSS2 cleaves viral spike protein and is a cofactor to ACE-2 for viral entry. It is a crucial serine protease for SARS-CoV-2 invasion [36].

In a gene expression analysis study of TMPRSS2, the Gene Expression Omnibus (GEO) dataset analysis in an experimentally induced periodontitis model showed increased TMPRSS2 expression in gingiva with periodontitis. The keratinocyte cell membrane of the periodontitis gingiva is strongly stained immunohistochemically for TMPRSS2 [13].

SARS-CoV-2 spike protein binds the cell membrane when activated by specific cellular enzymes like furin [28]. Furin cleaves the glycoprotein viral envelop, enhancing the viral fusion with the host cell membrane. Genomic characterization revealed that the furin enzyme might activate the specific site of the SARS-CoV-2 spike protein [27]. The furin cleavage site in the SARS-CoV-2 spike protein facilitates the virus-cell fusion [37]. This furin cleavage site is not found in SARS-CoV. Single-cell sequence dataset analysis found furin expression in potential target organs such as the lung, nose, heart, intestine, colon, rectum, and ileum [27]. Among the furin-expressing cells analyzed, epithelial cells make up more than 55% [27]. Sites with active periodontitis exhibit elevated expression of furin and cathepsin L proteases and may have an increased risk for virus binding and tissue infection [38].

3. Clinical studies associating periodontitis and COVID-19

Periodontitis can increase complications and the risk of death from COVID-19 (Table 1), and COVID-19 infection can aggravate periodontitis (Table 2). Research studies (Tables 1 and 2) in the form of prospective studies, retrospective studies, cross-sectional studies, longitudinal studies, case-control studies, case series, and case reports regarding this bidirectional relationship have been published. The statistical significance and the risk of morbidity and mortality were reported in these studies.

Table 1. Periodontitis associated with COVID-19 severity.

Study	Type	Time period	Location	Aim	COVID-19 patients	Comorbidities	Blood parameters	No. of patients	Periodontal diagnosis	Statistical significance	Conclusion
Alnomay et al. 2022 [39]	Retrospective cohort study	Jan 2020-Jul 2021	Saudi Arabia	To investigate the association between periodontitis and COVID-19 severity in the central region of Saudi Arabia	COVID-19 with periodontitis COVID-19 without periodontitis	Diabetes, Hypertension, Obesity and other comorbidities including respiratory disorders, endocrine disorders, cardiovascular disorders, cancer, kidney dialysis or organ transplant	C- reactive protein (CRP)	COVID patients: 188 Periodontitis: 99 No periodontitis: 89	Periodontitis	Periodontitis associated with covid-19 complications: Statistically significant	Periodontitis is significantly associated with a higher risk of developing COVID-19 complications, including the need for assisted ventilation, ICU admission, and death

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 May 2023 doi:10.20944/preprints202305.1601.v1

Cobas et al. 2022 [45]	Descriptive cross-sectional study	Mar 11, 2020- Mar 11, 2021	Cuba	To determine the relationship between self-reported periodontal disease, dental loss and COVID-19 activity	Patients infected with COVID-19 and survived	Hypertension, diabetes mellitus, heart disease, chronic respiratory disease, and morbid obesity	-	COVID infected and survived patients: 238	Periodontal disease and advanced periodontal disease (self-reported)	Periodontal disease and advanced periodontal disease associated with the severity of COVID-19: Not statistically significant	Periodontal disease and the severity of COVID-19 cannot be established
Costa et al. 2022 [41]	Short-term prospective study	Aug 2020- Mar 2021	Brazil	To assess the oral health conditions in COVID-19 patients and determine the association between oral health and disease outcomes, including the incidence of severe/critical symptoms, ICU admission	Hospitalized, infected COVID-19 patients with at least one typical COVID-19 symptoms	Hypertension, Obesity, Diabetes, COPD, Asthma, Cardiovascular diseases, Liver diseases, Cancer, Osteoporosis, Thyroid disease, Arthritis, HIV or other STD	-	128 patients	Periodontitis	Periodontitis and ICU admission, severe critical symptoms and invasive ventilation: Statistically significant	Periodontitis was associated with a higher occurrence of critical COVID-19 symptoms and the need for intensive medical care and death, even when adjusted for age and presence of comorbidities
Gupta et al. 2021 [42]	Cross-sectional analytical study	15 Jan 2021- 20 Feb 2021	India	To assess the association of periodontal health on the complicatio	COVID-19 patients	Diabetes, hypertension, pulmonary disease, chronic kidney disease, cancer, coronary artery disease, obesity	CRP, D-dimer, platelet count, ferritin, glycosylated hemoglobin (HbA1c),	82 patients	Stages of periodontitis I- IV	Stages of periodontitis and eventual survival, hospital admission, oxygen requirement, COVID-19	There is a direct association between periodontal disease and COVID-19-related outcomes

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 May 2023 doi:10.20944/preprints202305.1601.v1

				ns of COVID-19		and any other comorbidities	haemoglobin (Hb), vitamin D3, neutrophil/ lymphocyte ratio (N/L), troponin, procalcitonin and N-terminal-pro-brain natriuretic peptide (NT-proBNP)			pneumonia, D-dimer, troponin and pro-BNP: Statistically significant	
Larvin et al. 2020 [95]	National, longitudinal cohort study	Study recruitment: 2006-2010 Data extraction: till August 2020	UK	To quantify the impact of periodontal disease on COVID-19 infection and related outcomes utilizing the UK Biobank data	COVID-19 tested participants with self-reported history of periodontal disease COVID-19 tested participants with no self-reported history of periodontal disease	Cancer, hypertension, angina, cardiac arrest, diabetes, myocardial infarction, stroke, peripheral artery disease, atrial fibrillation, respiratory disease	Systolic and diastolic blood pressure and resting heart rate (biomarkers)	13,253 patients	Painful/ bleeding gums and loose teeth	Painful/ bleeding gums and mortality for participants with COVID-19 infection: Suggestive of risk (OR= 1.71)	There was a suggestive risk of mortality for COVID-19 positive participants with periodontal disease
Larvin et al. 2021 [47]	National, longitudinal cohort study	Study recruitment: 2006-2010 Data extraction: till August 2020	UK	To examine the impact of periodontal disease in obesity on COVID-19 infection and associated outcomes	Participants with records of COVID-19 test result and oral health status and body mass index (BMI) ≥18.5 kg/m²	Cancer, CVD, diabetes, hypertension, inflammatory disease and respiratory disease	Systolic and diastolic blood pressure and CRP	58,897 patients	Periodontal disease	The COVID-19 infection in individuals with periodontal disease in participants who were overweight:	Periodontal disease may exacerbate the effect of obesity on hospitalization and mortality following COVID-19 infection

 doi:10.20944/preprints202305.1601.v1

										Suggestive of risk (OR= 1.21) The COVID-19 infection in individuals with periodontal disease in participants who were obese: Suggestive of risk (OR= 1.37)	
Guardado-Luevanos I et al. 2022 [96]	Blinded case-control study	Dec 2020-Jan 2021	Mexico	To measure periodontal status through a previously validated test in individuals who were tested for SARS-CoV-2 infection	COVID-19 positive COVID-19 negative patients	-	-	COVID positive: 117 COVID negative: 117	Periodontal disease	Periodontal disease and SARS-CoV-2 positive individuals: Medium risk (OR= 3.3)	Self-reported periodontal disease can be an adjuvant marker to assume the risk of SARS-CoV-2 infection These individuals present more symptoms at the onset of the disease
Marouf et al. 2021[46]	Case-control study	27 Feb 2020- 31 Jul 2020	Qatar	To estimate the extent to which periodontitis is associated with COVID-19	COVID-19 positive patients with and without complications	Diabetes and comorbidities	HbA1C, Vit-D, lymphocyte, D-dimer, CRP, WBC	COVID-19 patients with complications: 40 (cases) COVID-19 patients without complication	Periodontitis	Periodontitis and risk of having COVID-19 complications: Medium risk (OR= 6.34)	Periodontitis was significantly associated with a higher risk of complications from COVID-19,

 doi:10.20944/preprints202305.1601.v1

				complications				s: 528 (controls)		Periodontitis and risk of having eventual death: High risk (OR=17.5)	including ICU admission, need for assisted ventilation and death
										Periodontitis and risk of having ICU admission: Medium risk (OR= 5.57)	Increased blood levels of markers linked with worse COVID-19 outcome were D-dimer, WBC and CRP
										Periodontitis and risk of needing assisted ventilation: Medium risk (OR=7.31)	
Mishra et al. 2022 [44]	Cross-sectional study	Apr 2021-Aug 2021	India	To determine whether an association exists between periodontitis and COVID-19	COVID-19 positive patients	Diabetes and Hypertension	-	294 patients	Stage I-IV periodontitis	Periodontitis and COVID-19 pneumonia: Statistically significant	Periodontitis is associated with severe COVID-19
Said et al. 2022 [40]	Case control study	Mar 1, 2020- Dec 31, 2020	Qatar	To test the hypothesis that a history of periodontal therapy could be associated with lower risk of COVID-19	Patients that experienced COVID-19-related complications such as ICU admission, mechanical ventilation and/or death and	Asthma, chronic respiratory diseases, chronic heart disease, diabetes, dermatitis, chronic liver disease, autoimmune diseases, solid organ transplant,	D-dimer, C-reactive protein (CRP), urea, creatinine, ferritin, interleukin-6 (IL-6), HbA1c, vitamin D, white	1325 patients (71 suffered severe COVID-19 complications)	Periodontitis (non-treated and treated)	Non-treated periodontitis and assisted ventilation: Statistically significant Non-treated periodontitis and D-dimer and ferritin:	COVID-19 patients with non-treated periodontitis (stages 2–4) were significantly more likely to need mechanical ventilation

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 May 2023 doi:10.20944/preprints202305.1601.v1

				complications	COVID-19 patients that recovered without major complications	peptic ulcer, immunosuppressive conditions, cancer, chronic kidney disease, hypertension, cerebrovascular accidents and deep vein thrombosis	blood cells (WBC) and lymphocytes		Statistically significant	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

Table 2. Effects of COVID-19 on periodontitis.

Study	Type	Time period	Location	Aim	COVID-19 patients	Comorbidities	No. of patients	Periodontal diagnosis	Results	Conclusion
Anand et al. 2021 [49]	Case control study	Aug 2020-Feb 2021	India	To determine whether periodontitis and poor oral hygiene are associated with COVID-19	COVID-19 patients	Diabetes, hypertension, neoplasia	COVID-19 positive patients: 79 COVID-19 negative patients: 71	Periodontitis	COVID-19 associated with periodontitis severity: Statistically significant COVID-19 and increased gingival inflammation: Statistically significant	SARS-CoV-2 infection may increase the prevalence and severity of periodontitis, as well as increase gingival inflammation, and is associated with poor oral hygiene

 doi:10.20944/preprints202305.1601.v1

Kaur et al. 2022 [43]	Comparative study	Mar 2021	India	To assess the correlation of COVID-19 infection and severity of periodontitis in subjects who had a mild form of the disease as compared to subjects having a moderate form of the disease and requiring hospitalization	Moderate COVID-19 patients recovering in COVID ward of the hospital Mild COVID-19 patients recovering at home	Diabetes	COVID-19 (moderate form of COVID) patients in the COVID ward of the hospital: 58 COVID-19 (mild form of COVID) patients at home: 58	Stages 0- 4 periodontal condition	The odds of getting severe periodontal disease were 6.32 times more in subjects with moderate COVID-19 compared to mild COVID-19 Moderate form of COVID-19 and periodontal disease severity: Statistically significant Stages 0-1 periodontal condition: The increased in HbA1C, lymphocyte and CRP of moderate compared to mild COVID-19: Statistically significant Stages 2-4 periodontal condition: The increased in HbA1C, lymphocyte, WBC and CRP of moderate compared to mild COVID-19: Statistically significant	Subjects with moderate form of COVID had more severe periodontitis

 doi:10.20944/preprints202305.1601.v1

Loukas et al. 2022 [50]	Case report	Jul 2020	Netherlands	To present a 38-year-old woman with generalized stage III, grade C periodontitis with a distorted post-operative blood clot formation who tested positive for COVID-19 after a periodontal surgery	-	No known prior comorbidities	1	Generalized stage III, grade C periodontitis with an abnormal post-operative blood clot formation	Initial phase: Uneventful 6 months follow-up: periodontal tissues responded favorably Surgical phase (1-4): 1.Upper right sextant: Healing uneventful 2. Lower right sextant: Healing uneventful 3.Upper anterior sextant: Day 1: No complaints **(COVID-19 diagnosis)** Day 2: Patient reported intraoral bleeding, fever, loss of taste, and abnormal blood clots Day 3: Bleeding noted, further suturing done Day 4: Patient reported no further bleeding	Abnormal postoperative bleeding tendency was associated with an active phase of COVID-19

 doi:10.20944/preprints202305.1601.v1

									4.Lower left posterior: Healing uneventful 6 months follow-up: Healing uneventful	
Manzalawi et al. 2020 [51]	Case series	Apr 2020-May 2020	Saudi Arabia	Three patients from three different Saudi cities who reported extensive gingival bleeding and pain preceding or coincidental with the confirmation of their COVID-19 infection	COVID-19 patients in hospital quarantine	No medical history	3	Gingival bleeding	The cases reported unprecedented profuse gingival bleeding that was not present before active signs of COVID-19 After COVID-19 infection subsided, gingival bleeding markedly declined	COVID-19 infection is associated with a heightened inflammatory reaction and clinical signs of profuse gingival bleeding

3.1. Periodontitis associated with COVID-19 Severity

Studies (Table 1) reported that periodontitis is significantly associated with COVID-19 complications, the severity of COVID-19 symptoms, the need for assisted ventilation, ICU admissions, and death [39–44]. Furthermore, COVID-19 patients with non-treated stage 2–4 periodontitis were significantly associated with an increased level of inflammatory biomarkers of COVID-19, such as D-dimer and ferritin [40]. Subjects with the moderate form of COVID-19 had more severe periodontitis when compared to those with the mild form of COVID-19 [43]. These collective studies appear to clearly demonstrate a biologic gradient for periodontitis severity and risk for progressive COVID-19. On the contrary, one study reported no statistical significance associated with COVID-19 and periodontitis; this could be attributed to the limitations of self-reported data on periodontal disease [45].

Of significance, COVID-19 patients with periodontitis have a high risk of mortality from COVID-19 and a medium risk of COVID-19 complications, ICU admission, and assisted ventilation [46]. There was a suggestive risk of periodontal disease in the obese, presenting a higher incidence of hospitalization and mortality from COVID-19 [47]. In patients with painful, bleeding gums and loose teeth, there was a suggestive risk of hospitalization and mortality following COVID-19 infection [48].

 doi:10.20944/preprints202305.1601.v1

3.2. Effects of COVID-19 on periodontitis

COVID-19 can exacerbate periodontal disease and inhibit periodontal healing, affecting patient's response to treatment (Table 2). In a case-control study, COVID-19 is significantly associated with periodontitis severity and increased gingival inflammation [49]. Furthermore, patients with a moderate form of COVID-19 had more severe forms periodontitis than those with a mild form of COVID-19 [43].

A case report of a 38-year-old woman with generalized stage III, grade C periodontitis reported abnormal postoperative bleeding after contracting COVID-19 right after periodontal surgery. This contrasts with her uneventful postoperative visits from previous periodontal surgeries. The patient was diagnosed with COVID-19 during the postoperative phase after the third periodontal surgery on the maxillary anterior sextant. Therefore, abnormal postoperative bleeding was reported to be associated with an active degree of COVID-19 [50].

In a case series of three systemically healthy patients who contracted COVID-19, these patients experienced gingival bleeding, which was not present before active signs of COVID-19. After the COVID-19 infection subsided, gingival bleeding markedly declined in these patients. This report suggested that gingival bleeding may be attributed to COVID-19 [51].

4. Inflammatory biomarkers involved in COVID-19

Inflammatory markers identified in COVID-19 included C-reactive protein (CRP), procalcitonin (PCT), IL-6, albumin, cytokines, serum amyloid A, serum ferritin, D-dimer, cardiac troponin, and renal biomarkers such as urea and creatinine [52–54]. The laboratory tests for infection and inflammation in COVID-19 are elevated for erythrocyte sedimentation rate (ESR), lactose dehydrogenase (LDH), leukocyte and platelet count.

The inflammatory markers positively correlated with the severity of COVID-19 included CRP [55], PCT, Interleukin 6 (IL-6) [56], and ESR. Biomarkers in COVID-19 can be helpful in the following areas: (1) early suspicion of disease; (2) confirmation and classification of disease severity; (3) framing hospital admission criteria; (4) identification of high-risk cohort; (5) framing ICU admission criteria; (6) rationalizing therapies; (7) assessing response to therapies; (8) predicting outcomes; (9) framing criteria for discharge from the ICU and hospital [55]. Interestingly, studies reporting COVID-19 biomarkers such as CRP, D-dimer, ferritin, PCT [56], N-terminal-pro-brain natriuretic peptide (NT-proBNP) [57,58], and IL-6 also found periodontal disease progression in these systemically healthy patients.

5. Inflammatory biomarkers linked with periodontitis

Periodontal inflammatory markers include serum and salivary biomarkers [59,60]. Serum biomarkers in periodontitis include TNF-α, IL1- [61–63], IL-6, CRP, surfactant protein-D, cortisol, osteocalcin, oncostatin M, albumin matrix metalloproteinases-3 (MMP-3), MMP-8, MMP-9 [64]. Salivary biomarkers in periodontitis include IL-6, IL1-beta, MMP-8, macrophage inflammatory protein-1 α, TNF- α, tissue inhibitor of metalloproteinases-1 (TIMP-1), receptor activator of nuclear factor kappa-B ligand (RANKL), lactate dehydrogenase (LDH), aspartate aminotransferase (AST) and alanine transaminase (ALT) [65]. Studies reported increasing these above-mentioned periodontal biomarkers in COVID-19 infection with associated comorbidities [66,67].

6. Inflammatory biomarkers associating periodontitis and COVID-19

Inflammatory biomarkers (Table 3) found in COVID-19 patients that have been associated with periodontal disease progression include C-reactive protein (CRP), D-dimer, ferritin, procalcitonin (PCT) and pro-brain natriuretic peptide (Pro-BNP) [57,58]. Elevation of these inflammatory COVID biomarkers could reduce extubation survival and prognosis, increase the risk of stroke and mortality, and increase the risk of developing acute respiratory disease syndrome (ARDS) and acute kidney injury [68]. HbA1C, lymphocyte, and CRP in periodontitis patients were significantly increased in the moderate form of COVID-19 compared to the mild form [43].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 May 2023 doi:10.20944/preprints202305.1601.v1

Table 3. Biomarkers found in COVID-19 and periodontal disease.

Biomarkers	Area affected	Clinical significance
COVID biomarkers associated with periodontal disease progression [69]		
CRP	Pulmonary function	Reduced extubation survival
	Neurological manifestation	Ischemic stroke occurrence
D-dimer	Pulmonary function	Reduced extubation survival
	Cardiovascular function	Poorer prognosis
	Coagulation and hemostasis	Risk of mortality
	Neurological manifestation	Ischemic stroke occurrence
Ferritin	Pulmonary function	ARDS development
PCT	Inflammation and infection	Severity and risk of mortality
	Neurological manifestation	Ischemic stroke occurrence
	Kidney and liver function	Acute kidney injury
Pro-BNP	Cardiovascular function	Poorer prognosis
Periodontitis biomarkers increased by COVID-19 infections		
AST [68]	Periodontium	Increased probing depths Clinical attachment loss
IL-1β [61,62]	Periodontium	Increased probing depths Clinical attachment loss
	Immune system	Autoimmune disorder Osteoarthritis
	Glucose metabolism	Insulin resistance
	Cardiovascular function	Acute ischemic events
TNF-α [70–72]	Periodontium	Increased probing depths Clinical attachment loss
	Immune system	Autoimmune disorder Rheumatoid arthritis Inflammatory bowel disease Noninfectious uveitis
	Cardiovascular function	Atherosclerotic lesions Vascular dysfunction Hypertension
	Glucose metabolism	Insulin resistance
	Lipid metabolism	Formation of atherogenic plaque

Bidirectionally, periodontitis biomarkers can be increased by COVID-19 infections [68]. These periodontitis biomarkers in COVID-19 patients can contribute to periodontitis disease progression in these patients [69]. These periodontitis markers include aspartate aminotransferase (AST), IL-1β [61,62], and TNF-α [70–72]. Elevation of these periodontitis biomarkers could increase the probing depth and clinical attachment loss, insulin resistance, acute ischemic events, autoimmune disorders, osteoarthritis, rheumatoid arthritis, inflammatory bowel disease, noninfectious uveitis, atherosclerotic lesions, vascular dysfunction, and hypertension [69].

 doi:10.20944/preprints202305.1601.v1

6.1. C-reactive protein

CRP is increased in acute infections and inflammation. CRP is produced by hepatocytes. CRP is an inflammatory marker that is detected in the plasma when there is inflammation [73]. CRP is increased in COVID-19 pneumonia [74]. Increased CRP levels in patients with COVID-19 are correlated with worse periodontal outcomes. CRP secretion commences 4–10 hours after an inflammatory stimulus, peaking at 48 hours, and has a half-life of 19 hours.

Increased CRP associated with worse outcomes may be correlated to a COVID-19-related "cytokine storm." When evaluating a range of hematological and immunological markers, it was found that CRP was one of the markers predictive of death from COVID-19 [75]. Patients with periodontitis reported a higher risk of COVID-19 complications and a higher level of CRP [46]. There was a statistically significant link between CRP levels and the different stages of periodontitis [43].

6.2. D-dimer

D-dimer is a by-product of blood clotting. The clinical significance of D-dimer is related to pulmonary embolism, deep vein thrombosis, and disseminated intravascular coagulation [59]. D-dimer is a marker for fibrin production; high D-dimer levels indicate hypercoagulability of the blood.

In a case-control study, it was reported that D-dimer levels were elevated in patients with COVID-19 infection and became significantly higher with critical illness [76]. D-dimer was also observed in higher concentrations in chronic periodontitis [77]. Similarly, COVID-19 patients with documented periodontal care had significantly lower D-dimer levels than COVID-19 patients without [40]. The D-dimer levels in periodontitis have been significantly correlated with a higher risk of COVID-19 complication [40,42,46].

6.3. Ferritin

Human ferritin is composed of a ferritin heavy chain (FTH) and a ferritin light chain (FTL). The synthesis of ferritin is regulated by nitrous oxide, glutathione, and other "reactive oxygen species." An increased ferritin level indicates activation of the monocyte-macrophage system. The magnitude of inflammation reflected by high ferritin levels at the admission of COVID-19 patients is independently predictive of in-hospital mortality [78].

6.4. Procalcitonin

PCT is a precursor of calcitonin and has been used as a biomarker for the diagnosis of bacterial infection. PCT has shown clinical significance by providing physicians with a positive correlation between disease severity and elevated PCT serum levels in patients [79]. The mean serum PCT levels were over four times greater in severe COVID-19 patients than in moderate COVID-19 patients [80]. The PCT levels were over eight times higher in critical COVID-19 patients than in moderate COVID-19 patients. High PCT levels have been associated with high rates of severe COVID-19 infections in patients admitted to the emergency department [81].

6.5. Pro-BNP

Patients with elevated levels of NT-proBNP values have a significantly increased risk of death from COVID-19 compared to patients with lower values [82,83]. The plasma NT-proBNP values were mainly related to the severity of pneumonia [83]. The serum levels of pro-BNP were also reported to be associated with periodontitis [84–87].

7. Herpesvirus reactivation linking periodontitis and COVID-19

Herpesvirus infection and their reactivation have been reported in varying degrees of COVID-19 severity. Viral coinfection [14,88] and active herpesviruses [15] have also been reported in aggressive periodontitis.

In severe COVID-19 patients admitted to the Intensive care unit (ICU), reactivation of herpes simplex virus (HSV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human herpesvirus 6 (HHV-6) have been reported [89–91]. Covid-19 patients with severe infection had a higher rate of positive EBV DNA compared to patients with mild symptoms. The median EBV DNA levels were also significantly higher in the severe COVID-19 patients compared to the mild COVID-19 patients [92]. In a cross-sectional study of mild to severe COVID-19 patients, the patient group with EBV viremia reported more severe pneumonia than the EBV-negative group [93]. On the other hand, non-geriatric patients with severe COVID-19 presented with high prevalence of CMV-seropositivity compared to patients with mild COVID-19. Interestingly, CMV-seropositivity was not significant in older patients with COVID-19. Thus, CMV-seropositivity may be a potential risk factor for severe COVID-19 in non-geriatric individuals [94].

Herpesvirus reactivation [15] and coinfections [14,88] have been linked to aggressive forms of periodontal disease. Reactivation of these herpesviruses by COVID-19 infections may have the potential to aggravate aggressive periodontitis towards rapid attachment loss and bone loss. It may also have the potential to aggravate chronic or quiescent periodontitis towards more attachment loss and bone loss.

It is well known in medicine that viral synergistic infections potentiate one or more of the indicated viral etiologic agents.

8. Conclusion

The most important finding of this literature review is to provide evidence for the increased risk of mortality and accompanying undesirable complications from COVID-19 in patients with periodontitis. Proper periodontal management with periodontal therapy and oral health maintenance may reduce death from COVID-19 infections and complications. Therefore, it is essential to understand the bidirectional relationship between periodontitis and COVID-19 infections. Better management of COVID-19 patients with periodontitis and periodontitis patients with COVID-19 may reduce the morbidity and mortality from COVID-19.

References

1. WHO. Coronavirus. (2021, June 14). https://www.who.int/health-topics/coronavirus#tab=tab_1 [Accessed on January 4, 2023].
2. Ting M, Suzuki JB. SARS-CoV-2: Overview and Its Impact on Oral Health. Biomedicines. 2021;9(11).
3. Ting, M.; Suzuki, J.B. COVID-19: Current Overview on SARS-CoV-2 and the Dental Implications. Oral health 2022, July https://www.oralhealthgroup.com/features/covid-19-current-overview-on-sars-cov-2-and-the-dental-implications/.
4. Ting, M.; Suzuki, J.B. Is the COVID-19 Pandemic Over? The Current Status of Boosters, Immunosenescence, Long Haul COVID, and Systemic Complications. Int. J. Transl. Med. 2022, 2, 230-241. https://doi.org/10.3390/ijtm2020021
5. Madi M, Abuohashish HM, Attia D, AlQahtani N, Alrayes N, Pavlic V, et al. Association between Periodontal Disease and Comorbidities in Saudi's Eastern Province. Biomed Res Int. 2021;2021:5518195.
6. Ejaz H, Alsrhani A, Zafar A, Javed H, Junaid K, Abdalla AE, et al. COVID-19 and comorbidities: Deleterious impact on infected patients. Journal of infection and public health. 2020;13(12):1833-9.
7. Muñoz Aguilera, E., Suvan, J., Orlandi, M., Miró Catalina, Q., Nart, J., & D'Aiuto, F. (2021). Association Between Periodontitis and Blood Pressure Highlighted in Systemically Healthy Individuals. Hypertension, 77(5), 1765–1774. https://doi.org/10.1161/hypertensionaha.120.16790.
8. Leong, X. F., Ng, C. Y., Badiah, B., & Das, S. (2014). Association between Hypertension and Periodontitis: Possible Mechanisms. The Scientific World Journal, 2014, 1–11. https://doi.org/10.1155/2014/768237.
9. Stewart R, West M. Increasing Evidence for an Association Between Periodontitis and Cardiovascular Disease. Circulation. 2016 Feb 9;133(6):549-51. doi: 10.1161/CIRCULATIONAHA.115.020869. Epub 2016 Jan 13. PMID: 26762522.
10. Periodontitis. (n.d.). https://www.ada.org/resources/research/science-and-research-institute/oral-health-topics/periodontitis [Accessed on January 4, 2023].
11. Mehrotra N, Singh S. Periodontitis. [Updated 2022 May 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK541126/.
12. Hajishengallis G. Periodontitis: from microbial immune subversion to systemic inflammation. Nature Reviews Immunology. 2015;15(1):30-44.

13. Ohnishi T, Nakamura T, Shima K, Noguchi K, Chiba N, Matsuguchi T. Periodontitis promotes the expression of gingival transmembrane serine protease 2 (TMPRSS2), a priming protease for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). J Oral Biosci. 2022 Jun;64(2):229-236. doi: 10.1016/j.job.2022.04.004. Epub 2022 Apr 25. PMID: 35472469; PMCID: PMC9035663.
14. Slots J. Herpesviral-bacterial interactions in periodontal diseases. Periodontol 2000. 2010;52(1):117-40.
15. Ting M, Contreras A, Slots J. Herpesviruses in localized juvenile periodontitis. 2000;35(1):17-25.
16. Ejaz H, Alsrhani A, Zafar A, Javed H, Junaid K, Abdalla AE, Abosalif KOA, Ahmed Z, Younas S. COVID-19 and comorbidities: Deleterious impact on infected patients. J Infect Public Health. 2020 Dec;13(12):1833-1839. doi: 10.1016/j.jiph.2020.07.014. Epub 2020 Aug 4. PMID: 32788073; PMCID: PMC7402107.
17. Mancini L, Quinzi V, Mummolo S, Marzo G, Marchetti E. Angiotensin-Converting Enzyme 2 as a Possible Correlation between COVID-19 and Periodontal Disease. Applied Sciences. 2020; 10(18):6224. https://doi.org/10.3390/app10186224.
18. Takahashi Y, Watanabe N, Kamio N, Yokoe S, Suzuki R, Sato S, Iinuma T, Imai K. Expression of the SARS-CoV-2 Receptor ACE2 and Proinflammatory Cytokines Induced by the Periodontopathic Bacterium Fusobacterium nucleatum in Human Respiratory Epithelial Cells. Int J Mol Sci. 2021 Jan 29;22(3):1352. doi: 10.3390/ijms22031352. PMID: 33572938; PMCID: PMC7866373.
19. To KK, Tsang OT, Yip CC, Chan KH, Wu TC, Chan JM, Leung WS, Chik TS, Choi CY, Kandamby DH, Lung DC, Tam AR, Poon RW, Fung AY, Hung IF, Cheng VC, Chan JF, Yuen KY. Consistent Detection of 2019 Novel Coronavirus in Saliva. Clin Infect Dis. 2020 Jul 28;71(15):841-843. doi: 10.1093/cid/ciaa149. PMID: 32047895; PMCID: PMC7108139.
20. Guo DF, Sun YL, Hamet P, Inagami T. The angiotensin II type 1 receptor and receptor-associated proteins. Cell Res. 2001 Sep;11(3):165-80. doi: 10.1038/sj.cr.7290083. PMID: 11642401.
21. Badran Z, Gaudin A, Struillou X, Amador G, Soueidan A. Periodontal pockets: A potential reservoir for SARS-CoV-2? Med Hypotheses. 2020 Oct;143:109907. doi: 10.1016/j.mehy.2020.109907. Epub 2020 May 30. PMID: 32504927; PMCID: PMC7833827.
22. Drozdzik A. Covid-19 and SARS-CoV-2 infection in periodontology: A narrative review. J Periodontal Res. 2022 Oct;57(5):933-941. doi: 10.1111/jre.13034. Epub 2022 Jul 15. PMID: 35839286; PMCID: PMC9350118.
23. Yuwa Takahashi, Norihisa Watanabe, Noriaki Kamio, Ryutaro Kobayashi, Toshimitsu Iinuma, Kenichi Imai, Aspiration of periodontopathic bacteria due to poor oral hygiene potentially contributes to the aggravation of COVID-19, Journal of Oral Science, 2021, Volume 63, Issue 1, Pages 1-3, Released on J-STAGE December 23, 2020, Advance online publication November 12, 2020, Online ISSN 1880-4926, Print ISSN 1343-4934, https://doi.org/10.2334/josnusd.20-0388, https://www.jstage.jst.go.jp/article/josnusd/63/1/63_20-0388/_article/-char/e.
24. Mahyuddin, AP, Kanneganti, A, Wong, JJL, et al. Mechanisms and evidence of vertical transmission of infections in pregnancy including SARS-CoV-2s. Prenatal Diagnosis. 2020; 40: 1655– 1670. https://doi.org/10.1002/pd.5765.
25. Bourgonje A.R., Abdulle A.E., Timens W., Hillebrands J.L., Navis G.J., Gordijn S.J., Bolling M.C., Dijkstra G., Voors A.A., Osterhaus A.D., et al. Angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 and the pathophysiology of coronavirus disease 2019 (COVID-19) J. Pathol. 2020 doi: 10.1002/path.5471.
26. Darbani B. The Expression and Polymorphism of Entry Machinery for COVID-19 in Human: Juxtaposing Population Groups, Gender, and Different Tissues. Int. J. Environ. Res. Public Heal. 2020;17:3433. doi: 10.3390/ijerph17103433.
27. Zhong, M., Lin, B., Pathak, J. L., Gao, H., Young, A. J., Wang, X., Liu, C., Wu, K., Liu, M., Chen, J., Huang, J., Lee, L., Qi, C., Ge, L., & Wang, L. (2020). ACE2 and Furin Expressions in Oral Epithelial Cells Possibly Facilitate COVID-19 Infection via Respiratory and Fecal–Oral Routes. Frontiers in Medicine, 7. https://doi.org/10.3389/fmed.2020.580796.
28. Sakaguchi W, Kubota N, Shimizu T, Saruta J, Fuchida S, Kawata A, Yamamoto Y, Sugimoto M, Yakeishi M, Tsukinoki K. Existence of SARS-CoV-2 Entry Molecules in the Oral Cavity. International Journal of Molecular Sciences. 2020; 21(17):6000. https://doi.org/10.3390/ijms21176000.
29. Zhao, D, Cheng, T, Koohi-Moghadam, M, et al. Salivary ACE2 and TMPRSS2 link to periodontal status and metabolic parameters. Clin Transl Disc. 2022; 2:e37. https://doi.org/10.1002/ctd2.37.
30. Ni, W., Yang, X., Yang, D. et al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. Crit Care 24, 422 (2020). https://doi.org/10.1186/s13054-020-03120-0.
31. Wrapp D, Wang N, Corbett K, Goldsmith J, Hsieh C, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020;367:1260–3.
32. PASTRIAN, S. G. Presence and expression of ACE2 receptor (Target of SARS-CoV-2) in human tissues and oral cavity. Possible routes infection in oral organs. Int. J. Odontostomat., 14(4):501-507, 2020.
33. Li H, Wu C, Yang Y, Liu Y, Zhang P, Wang Y, et al. Furin, a potential therapeutic target for COVID-19. ChinaXiv. (2020) 23:101642. doi: 10.1016/j.isci.2020.101642.
34. Ma Y, Hung Y, Wang T, Xiang AP, Huang W. ACE2 shedding and furin abundance in target organs may influence the efficiency of SARS-CoV-2 entry. ChinaXiv. (2020) 202002.00082. doi: 10.12074/202002.00082.

35. Xin L, GuangYou D, Wei Z, Jinsong S, JiaYuan C, Gao S, et al. A furin cleavage site was discovered in the S protein of the 2019 novel coronavirus. Chin J Bioinformatics. (2020) 18:103–08. doi: 10.12113/202002001.
36. Mancini, L., Americo, L. M., Pizzolante, T., Donati, R., & Marchetti, E. (2022). Impact of COVID-19 on Periodontitis and Peri-Implantitis: A Narrative Review. Frontiers in Oral Health, 3. https://doi.org/10.3389/froh.2022.822824.
37. Wu, C., Zheng, M., Yang, Y., Gu, X., Yang, K., Li, M., . . . Li, H. (2020). Furin: A Potential Therapeutic Target for COVID-19. iScience, 23(10), 101642. https://doi.org/10.1016/j.isci.2020.101642.
38. Bertolini M, Pita A, Koo S, Cardenas A, Meethil A. Periodontal disease in the COVID-19 era: potential reservoir and increased risk for SARS–CoV-2. Pesqui Bras Odontopediatria Clín Integr. 2020; 20(supp1):e0134. https://doi.org/10.1590/pboci.2020.162.
39. Alnomay N, Alolayan L, Aljohani R, Almashouf R, Alharbi G. Association between periodontitis and COVID-19 severity in a tertiary hospital: A retrospective cohort study. Saudi Dent J. 2022 Nov;34(7):623-628. doi: 10.1016/j.sdentj.2022.07.001. Epub 2022 Jul 27. PMID: 35915835; PMCID: PMC9327183.
40. Said KN, Al-Momani AM, Almaseeh JA, Marouf N, Shatta A, Al-Abdulla J, Alaji S, Daas H, Tharupeedikayil SS, Chinta VR, Hssain AA, Abusamak M, Salih S, Barhom N, Cai W, Sanz M, Tamimi F. Association of periodontal therapy, with inflammatory biomarkers and complications in COVID-19 patients: a case control study. Clin Oral Investig. 2022 Nov;26(11):6721-6732. doi: 10.1007/s00784-022-04631-6. Epub 2022 Jul 29. PMID: 35906340; PMCID: PMC9643194.
41. Costa CA, Vilela ACS, Oliveira SA, Gomes TD, Andrade AAC, Leles CR, Costa NL. Poor oral health status and adverse COVID-19 outcomes: A preliminary study in hospitalized patients. J Periodontol. 2022 Dec;93(12):1889-1901. doi: 10.1002/JPER.21-0624. Epub 2022 Jun 1. PMID: 35294780; PMCID: PMC9088593.
42. Gupta S, Mohindra R, Singla M, Khera S, Sahni V, Kanta P, Soni RK, Kumar A, Gauba K, Goyal K, Singh MP, Ghosh A, Kajal K, Mahajan V, Bhalla A, Sorsa T, Räisänen I. The clinical association between Periodontitis and COVID-19. Clin Oral Investig. 2022 Feb;26(2):1361-1374. doi: 10.1007/s00784-021-04111-3. Epub 2021 Aug 27. PMID: 34448073; PMCID: PMC8390180.
43. Kaur A, Sandhu HS, Sarwal A, Bhagat S, Dodwad R, Singh G, Gambhir RS. Assessment of correlation of COVID-19 infection and periodontitis- A comparative study. J Family Med Prim Care. 2022 May;11(5):1913-1917. doi: 10.4103/jfmpc.jfmpc_1978_21. Epub 2022 May 14. PMID: 35800529; PMCID: PMC9254790.
44. Mishra S, Gupta V, Rahman W, Gazala MP, Anil S. Association between Periodontitis and COVID-19 Based on Severity Scores of HRCT Chest Scans. Dent J (Basel). 2022 Jun 10;10(6):106. doi: 10.3390/dj10060106. PMID: 35735648; PMCID: PMC9222103.
45. Baganet-Cobas Y, Chaple-Gil AM, Caballero-Guerra Y, Chávez-Valdez D. Self-reported periodontal disease, dental loss and COVID-19 in older adults. Revista Cubana de Medicina Militar, 2022 Retrieved January 4, 2023, from https://pesquisa.bvsalud.org/portal/resource/pt/biblio-1408807.
46. Marouf N, Cai W, Said KN, Daas H, Diab H, Chinta VR, Hssain AA, Nicolau B, Sanz M, Tamimi F. Association between periodontitis and severity of COVID-19 infection: A case-control study. J Clin Periodontol. 2021 Apr;48(4):483-491. doi: 10.1111/jcpe.13435. Epub 2021 Feb 15. PMID: 33527378; PMCID: PMC8014679.
47. Larvin H, Wilmott S, Kang J, Aggarwal VR, Pavitt S, Wu J. Additive Effect of Periodontal Disease and Obesity on COVID-19 Outcomes. J Dent Res. 2021 Oct;100(11):1228-1235. doi: 10.1177/00220345211029638. Epub 2021 Jul 16. PMID: 34271846; PMCID: PMC8461046.
48. Larvin H, Wilmott S, Wu J, Kang J. The Impact of Periodontal Disease on Hospital Admission and Mortality During COVID-19 Pandemic. Front Med (Lausanne). 2020 Nov 23;7:604980. doi: 10.3389/fmed.2020.604980. PMID: 33330570; PMCID: PMC7719810.
49. Anand PS, Jadhav P, Kamath KP, Kumar SR, Vijayalaxmi S, Anil S. A case-control study on the association between periodontitis and coronavirus disease (COVID-19). J Periodontol. 2022 Apr;93(4):584-590. doi: 10.1002/JPER.21-0272. Epub 2021 Aug 24. PMID: 34347879.
50. Loukas G, Kosho MXF, Paraskevas S, Loos BG. Post-Operative Bleeding Complications in a Periodontitis Patient Testing Positive for COVID-19. Dent J (Basel). 2022 Jun 14;10(6):110. doi: 10.3390/dj10060110. PMID: 35735652; PMCID: PMC9222148.
51. Manzalawi, R, Alhmamey, K, Abdelrasoul, M. Gingival bleeding associated with COVID-19 infection. Clin Case Rep. 2021; 9: 294– 297. https://doi.org/10.1002/ccr3.3519.
52. Balta S, Balta I. COVID-19 and Inflammatory Markers. Curr Vasc Pharmacol. 2022;20(4):326-332. doi: 10.2174/1570161120666220404200205. PMID: 35379133.
53. Samprathi, M., & Jayashree, M. (2021). Biomarkers in COVID-19: An Up-To-Date Review. Frontiers in Pediatrics, 8. https://doi.org/10.3389/fped.2020.607647.
54. Furong Zeng, Yuzhao Huang, Ying Guo, Mingzhu Yin, Xiang Chen, Liang Xiao, Guangtong Deng. Association of inflammatory markers with the severity of COVID-19: A meta-analysis. International Journal of Infectious Diseases. Volume 96, 2020, Pages 467-474,ISSN 1201-9712. https://doi.org/10.1016/j.ijid.2020.05.055. (https://www.sciencedirect.com/science/article/pii/S1201971220303623).

55. Parimoo A, Biswas A, Baitha U, et al. (October 27, 2021) Dynamics of Inflammatory Markers in Predicting Mortality in COVID-19. Cureus 13(10): e19080. doi:10.7759/cureus.19080.
56. Marimuthu, Aishwarya K1,; Anandhan, Monisha2; Sundararajan, Lakshmikanthan2; Chandrasekaran, Jagadeesh1; Ramakrishnan, Balasubramaniam3. Utility of various inflammatory markers in predicting outcomes of hospitalized patients with COVID-19 pneumonia: A single-center experience. Lung India 38(5):p 448-453, September–October 2021. | DOI: 10.4103/lungindia.lungindia_935_20.
57. Gao, L., Jiang, D., Wen, Xs. et al. Prognostic value of NT-proBNP in patients with severe COVID-19. Respir Res 21, 83 (2020). https://doi.org/10.1186/s12931-020-01352-w.
58. Fazal I, Shetty B, Yadalam U, Khan SF, Nambiar M. Effectiveness of periodontal intervention on the levels of N-terminal pro-brain natriuretic peptide in chronic periodontitis patients. J Circ Biomark [Internet]. 2022 Oct. 3 [cited 2023 Jan. 27];11(1):48-56. Available from: https://journals.aboutscience.eu/index.php/jcb/article/view/2454.
59. Taba M, Kinney J, Kim AS, Giannobile WV. Diagnostic Biomarkers for Oral and Periodontal Diseases. Dental Clinics of North America. 2005;49(3):551-71.
60. Pavan Kumar A, Jagdish Reddy G, Raja babu P (2015). Biomarkers in periodontal disease. Dent Oral Craniofac Res 1: doi: 10.15761/DOCR.1000111.
61. Kaneko, N., Kurata, M., Yamamoto, T. et al. The role of interleukin-1 in general pathology. Inflamm Regener 39, 12 (2019). https://doi.org/10.1186/s41232-019-0101-5
62. Dinarello, C.A. (2011), A clinical perspective of IL-1β as the gatekeeper of inflammation. Eur. J. Immunol., 41: 1203-1217. https://doi.org/10.1002/eji.201141550.
63. Hönig, J., Rordorf-Adam, C., Siegmund, C., Wiedemann, W. and Erard, F. (1989), Increased interleukin-1 beta (IL-1β) concentration in gingival tissue from periodontitis patients. Journal of Periodontal Research, 24: 362-367. https://doi.org/10.1111/j.1600-0765.1989.tb00883.x.
64. Stathopoulou PG, Buduneli N, Kinane DF. Systemic Biomarkers for Periodontitis. Current Oral Health Reports. 2015;2(4):218-26.
65. Cafiero C, Spagnuolo G, Marenzi G, Martuscelli R, Colamaio M, Leuci S. Predictive Periodontitis: The Most Promising Salivary Biomarkers for Early Diagnosis of Periodontitis. 2021;10(7):1488.
66. Gelzo M, Cacciapuoti S, Pinchera B, De Rosa A, Cernera G, Scialò F, et al. Matrix metalloproteinases (MMP) 3 and 9 as biomarkers of severity in COVID-19 patients. Scientific Reports. 2022;12(1):1212.
67. Al-Samkari H, Karp Leaf RS, Dzik WH, Carlson JCT, Fogerty AE, Waheed A, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood. 2020;136(4):489-500.
68. Mario Taba, J., Kinney, J., Kim, A. S., & Giannobile, W. V. (2005). Diagnostic Biomarkers for Oral and Periodontal Diseases. Dental clinics of North America, 49(3), 551. https://doi.org/10.1016/j.cden.2005.03.009.
69. Battaglini D, Lopes-Pacheco M, Castro-Faria-Neto HC, Pelosi P, Rocco PRM. Laboratory Biomarkers for Diagnosis and Prognosis in COVID-19. Front Immunol. 2022 Apr 27;13:857573. doi: 10.3389/fimmu.2022.857573. PMID: 35572561; PMCID: PMC9091347.
70. Popa, C., Netea, M. G., van Riel, P. L., van der Meer, J. W., & Stalenhoef, A. F. (2007). The role of TNF-α in chronic inflammatory conditions, intermediary metabolism, and cardiovascular risk. Journal of Lipid Research, 48(4), 751–762. https://doi.org/10.1194/jlr.r600021-jlr200.
71. Jang DI, Lee AH, Shin HY, Song HR, Park JH, Kang TB, Lee SR, Yang SH. The Role of Tumor Necrosis Factor Alpha (TNF-α) in Autoimmune Disease and Current TNF-α Inhibitors in Therapeutics. Int J Mol Sci. 2021 Mar 8;22(5):2719. doi: 10.3390/ijms22052719. PMID: 33800290; PMCID: PMC7962638.
72. Urschel K, Cicha I. TNF-α in the cardiovascular system: from physiology to therapy. International Journal of Interferon, Cytokine and Mediator Research. 2015;7:9-25. https://doi.org/10.2147/IJICMR.S64894.
73. Sarhat, Entedhar & Zbaar, Sami & Ahmed, Shaimaa & Ahmed, Takea & Sarhat, Thuraia. (2021). Salivary biochemical variables of Liver Function in among Individuals with COVID-19 in Thi-Qar Province. Egyptian Journal of Chemistry. 10.21608/ejchem.2021.100246.4767.
74. Chen W, Zheng KI, Liu S, Yan Z, Xu C, Qiao Z. Plasma CRP level is positively associated with the severity of COVID-19. Ann Clin Microbiol Antimicrob. 2020 May 15;19(1):18. doi: 10.1186/s12941-020-00362-2. PMID: 32414383; PMCID: PMC7227180.
75. Stringer D, Braude P, Myint PK, Evans L, Collins JT, Verduri A, et al. The role of C-reactive protein as a prognostic marker in COVID-19. International Journal of Epidemiology. 2021;50(2):420-9.
76. Yao Y, Cao J, Wang Q, Shi Q, Liu K, Luo Z, et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. Journal of Intensive Care. 2020;8(1):49.
77. Dikshit S. Fibrinogen Degradation Products and Periodontitis: Deciphering the Connection. J Clin Diagn Res. 2015 Dec;9(12):ZC10-2. doi: 10.7860/JCDR/2015/14729.6922. Epub 2015 Dec 1. PMID: 26816985; PMCID: PMC4717699.
78. Bo Zhou, Jianqing She, Yadan Wang et al. Utility of Ferritin, Procalcitonin, and C-reactive Protein in Severe Patients with 2019 Novel Coronavirus Disease, 19 March 2020, PREPRINT (Version 1) available at Research Square [https://doi.org/10.21203/rs.3.rs-18079/v1].

79. Cleland DA, Eranki AP. Procalcitonin. [Updated 2022 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539794/.
80. Hu R, Han C, Pei S, Yin M, Chen X. Procalcitonin levels in COVID-19 patients. International Journal of Antimicrobial Agents. 2020;56(2):106051.
81. Tong-Minh K, van der Does Y, Engelen S, de Jong E, Ramakers C, Gommers D, et al. High procalcitonin levels associated with increased intensive care unit admission and mortality in patients with a COVID-19 infection in the emergency department. BMC Infectious Diseases. 2022;22(1):165.
82. Gao L, Jiang D, Wen X-s, Cheng X-c, Sun M, He B, et al. Prognostic value of NT-proBNP in patients with severe COVID-19. Respiratory Research. 2020;21(1):83.
83. Wang L, Chen F, Bai L, Bai L, Huang Z, Peng Y. Association between NT-proBNP Level and the Severity of COVID-19 Pneumonia. Cardiology Research and Practice. 2021;2021:5537275.
84. Leira Y, Blanco J. Brain natriuretic peptide serum levels in periodontitis. J Periodontal Res. 2018 Aug;53(4):575-581. doi: 10.1111/jre.12547. Epub 2018 Apr 6. PMID: 29633261.
85. Leira Feijóo, Yago & Blanco, Juan. (2018). Brain natriuretic peptide serum levels in periodontitis. Journal of Periodontal Research. 53. 10.1111/jre.12547.
86. Vijayaraj, S., Ari, G., Rajendran, S., Mahendra, J., & Namasivayam, A. (2022). Comparison of the Serum and Salivary Levels of NT-proBNP in Systemically Healthy Subjects with Mild, Moderate and Severe Chronic Periodontitis. International Journal Of Drug Research And Dental Science, 4(1), 40-48. https://doi.org/10.36437/ijdrd.2022.4.1.F.
87. Molinsky RL, Yuzefpolskaya M, Norby FL, Yu B, Shah AM, Pankow JS, et al. Periodontal Status, C-Reactive Protein, NT-proBNP, and Incident Heart Failure: The ARIC Study. JACC: Heart Failure. 2022;10(10):731-41.
88. Contreras A, Slots J. Herpesviruses in human periodontal disease. J Periodontal Res. 2000;35(1):3-16.
89. Simonnet A, Engelmann I, Moreau AS, Garcia B, Six S, El Kalioubie A, et al. High incidence of Epstein–Barr virus, cytomegalovirus, and human-herpes virus-6 reactivations in critically ill patients with COVID-19. Infectious Diseases Now. 2021;51(3):296-9.
90. Saade A, Moratelli G, Azoulay E, Darmon M. Herpesvirus reactivation during severe COVID-19 and high rate of immune defect. Infectious Diseases Now. 2021;51(8):676-9.
91. Zubchenko S, Kril I, Nadizhko O, Matsyura O, Chopyak V. Herpesvirus infections and post-COVID-19 manifestations: a pilot observational study. Rheumatol Int. 2022;42(9):1523-30.
92. Paolucci S, Cassaniti I, Novazzi F, Fiorina L, Piralla A, Comolli G, et al. EBV DNA increase in COVID-19 patients with impaired lymphocyte subpopulation count. Int J Infect Dis. 2021;104:315-9.
93. Im JH, Nahm CH, Je YS, Lee JS, Baek JH, Kwon HY, et al. The effect of Epstein-Barr virus viremia on the progression to severe COVID-19. Medicine (Baltimore). 2022;101(18):e29027.
94. Weber S, Kehl V, Erber J, Wagner KI, Jetzlsperger AM, Burrell T, et al. CMV seropositivity is a potential novel risk factor for severe COVID-19 in non-geriatric patients. PLoS One. 2022;17(5):e0268530.
95. Larvin H, Wilmott S, Wu J, Kang J. The Impact of Periodontal Disease on Hospital Admission and Mortality During COVID-19 Pandemic. Front Med (Lausanne). 2020;7:604980.
96. Guardado-Luevanos I, Bologna-Molina R, Zepeda-Nuño JS, Isiordia-Espinoza M, Molina-Frechero N, González-González R, Pérez-Pérez M, López-Verdín S. Self-Reported Periodontal Disease and Its Association with SARS-CoV-2 Infection. Int J Environ Res Public Health. 2022 Aug 18;19(16):10306. doi: 10.3390/ijerph191610306. PMID: 36011941; PMCID: PMC9407774.