QUALITY IMPROVEMENT IN DENTAL AND MEDICAL KNOWLEDGE, RESEARCH, SKILLS AND ETHICS FACING GLOBAL CHALLENGES

Edited by
Armelia Sari Widyarman, Muhammad Ihsan Rizal,
Moehammad Orliando Roeslan & Carolina Damayanti Marpaung

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Armelia Sari Widyarman, Muhammad Ihsan Rizal, Moehammad Orliando Roeslan and Carolina Damayanti Marpaung
Universitas Trisakti, Indonesia

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Periodontitis effects toward the extent of COVID-19 severity (Scoping review)

S.A. Arthur
Faculty of Dentistry, Trisakti University, Jakarta, Indonesia

M. Louisa
Department of Periodontology, Faculty of Dentistry, Trisakti University, Jakarta, Indonesia

ABSTRACT: In December 2019, SARS-CoV-2 started spreading in China, subsequently causing a worldwide COVID-19 pandemic that affects various organs, predominantly respiration. Periodontitis, a chronic inflammation disease of periodontal tissues, also alters our systemic immune response. Consequently, periodontitis is presumed to play a part in COVID-19 severity. This research was conducted to ascertain different research methods implemented to determine periodontitis effects toward COVID-19 severity, and also blood parameters, biomarkers, and COVID-19 severity parameters which were significantly contrasting in COVID-19 patients with periodontitis. This scoping review was carried out utilizing the PRISMA diagram consisting of literature associated with COVID-19 patients as a population, the impact of periodontitis on COVID-19 severity as the concept, and a global context in several databases, including PubMed, WILEY, and Google Scholar. Five journals in line with the inclusion criteria applied confirmed various affiliations between periodontitis and COVID-19 severity. Journals included were one cross-sectional study, two cohorts, one case-control, and one analytical retrospective study. These studies stated that COVID-19 severity was predicated on several parameters, including blood parameters, biomarkers, hospitalization, mortality, ICU support, and ventilation assistance. Research methods implemented on periodontitis effects toward COVID-19 severity were case-control, cohort, cross-sectional, and analytical retrospective studies. Periodontitis aggravates COVID-19 severity as a result of increased parameters (D-dimer, troponin, CRP, pro-BNP, procalcitonin, HbA1c, ferritin, and WBC), consequently increasing hospitalization rate, mortality, ICU support, and ventilation assistance.

1 BACKGROUND

In December 2019, a sequence of respiratory diseases dispersed in Wuhan, China, that gave rise to Coronavirus disease 2019 (COVID-19) which was then set as a pandemic by the World Health Organization (WHO) (Soy *et al.* 2020; Yuki *et al.* 2020). The cause of this disease, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) gains entrance into host cells through the binding of spike protein and angiotensin-converting enzyme 2 (ACE2) which are found on cardiac, renal, intestinal, endothelial cells, and alveolar type II cell surfaces (Azer 2020; Soy *et al.* 2020). The virus mainly enters through the lung and spreads toward other organs by means of blood circulation, which could cause organ dysfunction and death (Garcés Villalá *et al.* 2020). COVID-19 major manifestations include fever, fatigue, and dry cough (National Health Commission & National Administration of Traditional Chinese Medicine 2020). Based on its clinical manifestation, COVID-19 cases

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are divided into asymptomatic, mild, moderate, severe, and critical cases. Critical cases are indicated by the presence of respiratory failure, assisted ventilation, shock, and organ failures that necessitates ICU admission (Marzano *et al.* 2021; National Health Commission & National Administration of Traditional Chinese Medicine 2020).

Periodontal disease is a chronic inflammatory disease of periodontium, and acts as the main reason underlying tooth loss with a prevalence constituting 20%–50% of the global population (Nazir 2017). Two main periodontal diseases are gingivitis and periodontitis (Shaw *et al.* 2016). Gingivitis (gingival inflammation response) otherwise healed could progress into periodontitis which imposes degradation of periodontal tissue (Belstrøm *et al.* 2017). Besides the local effect generated, periodontitis also increases C-reactive protein (CRP), acute phase proteins, plasma antibody levels, coagulation factors, white blood cell (WBC), and proinflammatory cytokines (interleukin / IL-1β, IL-2, IL-6, Interferon / IFN – γ, and tumor necrosis factor / TNF- α) (Fabri 2020).

There are a lot of various biological possibilities that underlie the association between these two diseases. There is a similar inflammatory pathway between COVID-19 and periodontitis, which is shown by the increase of proinflammatory cytokines (IL-1β, IL-2, IL-6, TNF- α, IFN-γ), CRP, acute phase proteins, and coagulation factors (Fabri 2020). COVID-19-induced cytokine storm is comparable to cytokine imbalance manifested in periodontitis, thus there is a potential relationship between periodontitis and COVID-19 complications (Martu *et al.* 2020).

ACE (main receptors for SARS-CoV-2) are also found in the oral epithelial cells, such as the tongue, buccal mucosa, gingival tissue, periodontal pockets, and gingival crevices (Sukumar & Tadepalli 2021). Periodontal pockets could also be an advantageous setting for SARS-CoV-2 replication and survival (Deo *et al.* 2021). The binding between SARS-CoV-2 and ACE2 serves as a cellular entrance that facilitates virus entry and increases the viral load in the tissue (Ciornei 2020). Plasma viral load increase is significantly linked with the increase of inflammatory markers and COVID-19 severity (Fajnzylber *et al.* 2020). Pneumonia is also one of the poor COVID-19 severity indicators (Yuki *et al.* 2020). Periodontopathic bacteria are also found in the bronchoalveolar lavage fluid (BALF) of pneumonia patients. An increase of periodontopathic bacteria could intensify COVID-19 severity through several mechanisms, involving an increase of ACE2 expression, proinflammatory cytokines increase in the lower respiratory tract, and periodontopathic bacteria proteases that could facilitate SARS-CoV-2 infection by degrading S protein in SARS-CoV-2 (Takahashi *et al.* 2021a).

Several associations pertaining to periodontitis that may potentially increase COVID-19 severity stated above urges the writer's interest in conducting a scoping review based on periodontitis impact toward COVID-19 severity. The objective of this study is to see various methods done on this topic, as well as blood parameters, biomarkers, and COVID-19 severity parameters which were remarkably distinct in COVID-19 patients with periodontitis. This study aspires to be an educational means for both professional health workers and the general public, and also help to identify individuals at more vulnerable risk of COVID-19 severity.

2 METHODS

This research is done by a researcher between August and December 2021, using scoping review method by means of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagrams. The search strategy is done by using population, concept, and context criteria, and inclusion and exclusion criteria by using the Boolean search on three databases as listed in Table 1. Search results on three databases obtained as much as 698 journals (31 journals from PubMed, 32 journals from WILEY, and 635 journals from Google Scholar). Out of a number of 698 journals, 46 duplicates were discovered, leaving

652 journals which were then further sorted and assessed based on their title and abstract. A sum of 647 articles was excluded, of which 64 articles did not have any association with periodontitis, 31 articles did not have any association with COVID-19 severity, 395 articles did not have both association with periodontitis and COVID-19 severity, 12 journals could not be accessed, 23 articles were response articles, 46 articles were written in languages apart from Indonesian and English, 24 weren't an article/journal (website, posters, magazines, and so forth), 43 were reviews, and 9 articles didn't contain any clinical data. Through full-text reading of five articles, no additional articles were excluded.

Table 1. Search strategy.

Search strategy
PCC criteria: – Population: literature associated with COVID-19 patients – Concept: periodontitis impact toward COVID-19 severity – Context: global
Electronic database: Google Scholar, PubMed, WILEY
Inclusion criteria: Original articles obtained from PubMed, Google Scholar, and WILEY; cohorts, case controls, case reports, cross-sectionals, randomized controlled trials, journals, and grey literature written in English and Indonesian, journals published since 2020
Exclusion criteria: Response articles, systematic reviews, journals, and grey literature written in languages aside from English and Indonesian
Boolean search : ("Periodontal disease" OR "Periodontal manifestation" OR periodontitis) AND ("COVID-19 severity" OR "COVID-19 complications" OR "COVID-19 outcomes" OR "COVID-19 aggravation" OR "COVID-19 disease" OR "COVID-19 exacerbation" OR "worsen COVID-19")

3 MAIN FINDINGS

The research concludes with five full-text journals acquired and used in this research. The PRISMA diagram denotes the flow of the searching and sorting phase, which is displayed in Figure 1. Table 2 represents relevant findings taken from each study.

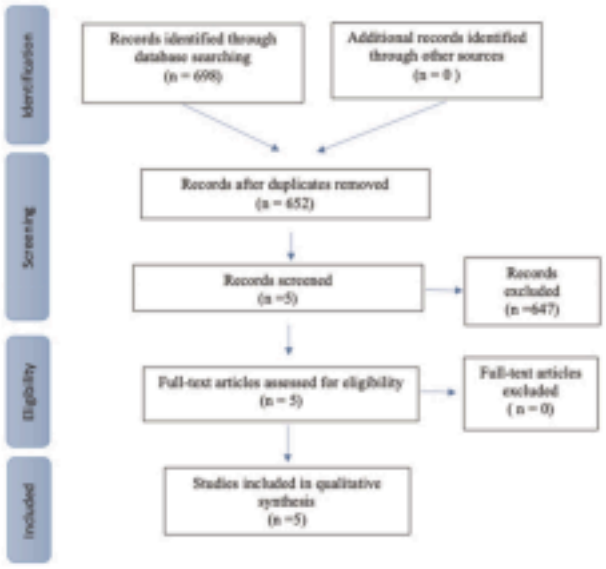

Figure 1. Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA).

Table 2. Extraction table.

Authors	Year	Title	Objectives	Sample group	Study design	Research result
Gupta *et al.*	2021	The clinical association between periodontitis and COVID-19.	Association between periodontitis and COVID-19 clinical symptoms	82 COVID-19 positive patients	Cross sectional	Periodontitis impact both direct and indirect toward a worse prognosis of COVID-19
Larvin *et al.*	2021	Additive effect of periodontal disease and obesity on COVID-19 outcomes.	Additive effects of periodontal disease and obesity toward COVID-19	58,897 data obtained from the UK Biobank cohort study between March 2020 and February 2021	Cohort	Periodontal disease could worsen obesity effect toward COVID-19 hospitalization and mortality
Larvin *et al.*	2020	The impact of periodontal disease on hospital admission and mortality during COVID-19 pandemic.	To ascertain periodontal disease impact toward COVID-19 patients' hospitalization and mortality	13,253 data obtained from the UK Biobank cohort study between March and June 2020	Cohort	No heightened risk of mortality and hospitalization of COVID-19 patients with loose teeth as an indicator of periodontal disease
Marouf *et al.*	2021	Association between periodontitis and severity of COVID-19 infection: A case-control study.	Association between periodontitis and COVID-19 complications	Electronic health data of 568 COVID-19 patients with active dental records	Case control	Association between periodontitis and elevated risk of COVID-19 complications (ICU admission, need for assisted ventilation, death, and biomarker elevation)
Sirin & Ozcelik	2021	The relationship between COVID-19 and the dental damage stage was determined by radiological examination.	Link between dental damage stage and COVID-19 severity	Dental Damage Stage data based upon Apical Periodontitis Grading Scale, Radiologic Alveolar Bone Loss and Pathophysiological Process of Dental Caries from 137 COVID-19 positive patients	Analytical retrospective	Connection observed between dental damage stage and COVID-19 severity that is fit for extensive studies

Data obtained from full-text journals used in this study are then divided and categorized into several different categories which are displayed in different tables. Categories related to COVID-19 severity are divided into blood parameters and biomarkers, hospitalization, mortality, assisted ventilation, and ICU admission.

Two articles mentioned periodontitis's impact toward blood parameters and biomarkers which modify COVID-19 severity (Table 3). Research conducted by Gupta *et al.* (2021) stated that patients with periodontitis have higher levels of CRP, D-dimer, HbA1c, ferritin, troponin, pro-BNP, and procalcitonin. At the same time, Marouf *et al.* (2021) claimed that

heightened levels of HbA1c, WBC, and CRP are appeared in COVID-19 patients with periodontitis.

The association between periodontitis and the risk of COVID-19 hospitalization is shown in four articles (Table 4). A study conducted by Gupta *et al.* (2021) shows a heightened risk of hospitalization in patients with periodontitis. Table 4 mentions two separate researches carried out by Larvin *et al.* (2021, 2020), where both articles utilize data extracted from a UK Biobank cohort study which uses self-reported indicators by patients with bleeding and painful gums (mild to moderate periodontal disease indicator) and loose teeth (severe periodontal disease indicator).

Table 3. Blood parameters and biomarkers.

Authors	Sample group	Research results
Gupta *et al.*	82 COVID-19-positive patients (27 patients without periodontal disease, 21 patients with gingivitis, and 34 patients with stage I-IV periodontitis)	– Gingival recession and missing teeth on account of periodontal disease were related to D-dimer and troponin levels. – A significant association between probing depth and levels of HbA1c, CRP, D-dimer, and ferritin. – Higher clinical attachment loss (CAL) was connected to heightened levels of CRP, D-dimer, pro-BNP, troponin, and pro-calcitonin levels. – Patients with a higher degree of periodontitis severity have heightened D-dimer, pro-BNP, and troponin levels.
Marouf *et al.*	Electronic health data of 568 COVID-19-positive patients (258 patients with periodontitis)	Higher HbA1c, WBC, and CRP levels in COVID-19 patients with periodontitis compared to those without.

Table 4. Hospitalization.

Authors	Sample group	Research results
Gupta *et al.*	82 COVID-19-positive patients (27 patients without periodontal disease, 21 patients with gingivitis, and 34 patients with stage I-IV periodontitis)	COVID-19 patients with periodontitis had higher risk of hospitalization.
Larvin *et al.*	58,897 data obtained from the UK Biobank cohort study between March 2020 and February 2021 (14,466 positive COVID-19 cases, encompassing 6124 patients with bleeding gums, 1511 patients with loose teeth, 1397 patients with painful gums, and 49,565 patients without any history of periodontal disease)	Obese COVID-19 patients with periodontal disease had higher chance of hospitalization compared to obese COVID-19 patients without any periodontal disease.
Larvin *et al.*	13,253 data obtained from the UK Biobank cohort study between March and June 2020 (365 patients with painful gums, 1329 patients with bleeding gums, 406 patients with loose teeth, and 11,153 patients without any history of periodontal disease)	Loose teeth as a periodontal disease indicator wasn't associated with higher COVID-19 hospitalization.
Sirin & Ozcelik	Dental Damage Stage (DD Stg) data based upon Apical Periodontitis Grading Scale, Radiologic Alveolar Bone Loss dan Pathophysiological Process of Dental Caries from 137 COVID-19 positive patients	Patients expressing Dental Damage Stage (DD Stg) 2 and 3 had higher COVID-19 hospitalization in comparison to patients with DD Stg 0 and 1.

'Additive Effect of Periodontal Disease and Obesity on COVID-19 Outcomes' which studies 58897 data between March 2020 and February 2021 showed an increase in hospitalization in obese COVID-19 patients with periodontal disease indicators compared to those without obesity, which proves an evident additive effect between periodontal disease and obesity which exerts influence on COVID-19 severity (Larvin *et al.* 2021). However, contradictory to the journal previously mentioned, 'The impact of periodontal disease on hospital admission and mortality during COVID-19 pandemic' which utilized 13,253 data between March and June 2020 showed no association between loose teeth indicator with COVID-19 hospitalization (Larvin *et al.* 2020).

One study done by Sirin & Ozcelik (2021) explores the relation of COVID-19 severity with DD Stg (dental status indicator based on the summation of APGS, RBL, and PPDC scores which are then further categorized into four classifications, which are DD Stg 0 (healthy), DD Stg 1 (mild), DD Stg 2 (moderate) dan DD Stg 3 (severe). The study result shows that patients with DD Stg 2 and 3 exhibited higher hospitalization in contrast with patients with DD Stg 0 and 1.

Table 5 discusses the association between periodontitis and mortality of COVID-19 patients. A study conducted by Gupta *et al.* (2021) and Marouf *et al.* (2021) conveys that periodontitis increases the mortality rate in COVID-19 patients. Corresponding to this discovery, another study conducted by Sirin & Ozcelik (2021) found that patients with DD Stg 3 notably had higher mortality rates compared to lower DD Stg.

Another study conducted by Larvin *et al.* (2021) in 'Additive Effect of Periodontal Disease and Obesity on COVID-19 Outcomes' showed increased mortality risk in obese COVID-19 patients with periodontitis. Dissimilar to this finding, a different study conducted by Larvin *et al.* (2020) in 'The impact of periodontal disease on hospital admission and

Table 5. Mortality.

Authors	Sample group	Research results
Gupta *et al.*	82 COVID-19-positive patients (27 patients without periodontal disease, 21 patients with gingivitis, and 34 patients with stage I-IV periodontitis)	Patients with mortality had a greater degree of periodontitis severity.
Larvin *et al.*	58,897 data obtained from the UK Biobank cohort study between March 2020 and February 2021 (14,466 positive COVID-19 cases, encompassing 6124 patients experiencing bleeding gums, 1511 patients experiencing loose teeth, 1397 patients experiencing painful gums, and 49,565 patients without any history of periodontal disease)	Obese COVID-19 patients with periodontal disease had higher rates of mortality compared to obese COVID-19 patients without periodontal disease.
Larvin *et al.*	13,253 data obtained from the UK Biobank cohort study between March and June 2020 (365 patients experiencing painful gums, 1329 patients experiencing bleeding gums, 406 patients experiencing loose teeth, and 11,153 patients without any history of periodontal disease)	Loose teeth as a periodontal disease indicator did not have any relation with an increase in the mortality rate in COVID-19.
Marouf *et al.*	Electronic health data of 568 COVID-19-positive patients (258 patients with periodontitis)	Periodontitis was connected with an increased risk of mortality in COVID-19 patients.
Sirin & Ozcelik	Dental Damage Stage data based upon APGS, RBL, and PPDC scores obtained from 137 COVID-19-positive patients	Patients with DD Stg 3 had a significant increase in mortality rate.

mortality during COVID-19 pandemic' using different sample groups stated no association between loose teeth as a periodontal disease indicator with the mortality rate in COVID-19 patients.

Based on Table 6, studies done by Gupta *et al.* (2021) and Marouf *et al.* (2021) showed a relation between periodontitis with the need for assisted ventilation. This finding indicates that periodontitis is related to higher COVID-19 severity, owing to the fact that the need for ventilation assistance is a poorer COVID-19 severity indicator (National Health Commission & National Administration of Traditional Chinese Medicine 2020).

Table 6. Assisted ventilation.

Authors	Sample group	Research results
Gupta *et al.*	82 COVID-19-positive patients (27 patients without periodontal disease, 21 patients with gingivitis, and 34 patients with stage I-IV periodontitis)	A significant association between BOP, probing depth, gingival recession, CAL with oxygen requirement, and assisted ventilation in COVID-19 patients, particularly in patients exhibiting stage III and IV periodontitis.
Marouf *et al.*	Electronic health data of 568 COVID-19-positive patients (258 patients with periodontitis)	Association between periodontitis and the need for assisted ventilation.

Table 7 shows data from two studies conducted by Gupta *et al.* (2021) and Marouf *et al.* (2021), where both studies presented that periodontitis affects COVID-19 patients' ICU admission. Both studies connect periodontitis with COVID-19 severity, because ICU admission is considered one unfavorable COVID-19 severity indication (National Health Commission & National Administration of Traditional Chinese Medicine 2020).

Table 7. ICU admission.

Authors	Sample group	Research results
Gupta *et al.*	82 COVID-19-positive patients (27 patients without periodontal disease, 21 patients with gingivitis, and 34 patients with stage I-IV periodontitis)	COVID-19 patients with higher severity of periodontitis underwent ICU admission in contrast to those with healthy periodontal tissues which generally only encounter home isolation or ward admission.
Marouf *et al.*	Electronic health data of 568 COVID-19-positive patients (258 patients with periodontitis)	Periodontitis had a significant impact toward the need of assisted ventilation in COVID-19 patients.

Previous studies stated above have proven to validate the associations between periodontitis and COVID-19 severity. An earlier study conducted by Marouf *et al.* (2021) showed an association between periodontitis and higher mortality, especially if there are comorbidities involved. A Mendelian randomization study carried out by Wang *et al.* (2021) also discovered a significant association between genetically proxied periodontal disease with a heightened risk of COVID-19 susceptibility and hospitalization. A study conducted by Takahashi *et al.* (2021a) also found culture supernatant *Fusobacterium nucleatum* (CSF) effect on the increase of ACE2 expression, IL-6, and IL-8 in COVID-19 patients. This finding reinforces the hypothesis stating that periodontopathic bacteria increase can cause poorer COVID-19 severity (Takahashi *et al.* 2021b).

3.1 *Periodontitis effects toward biomarkers in COVID-19 patients*

Out of 698 journals, 46 duplicates were discovered and further 647 journals were excluded, leaving five full-text articles deemed relevant. Five articles mentioned used various research methods, consisting of one cross-sectional, two cohorts, one case-control, and one analytical retrospective study. This scoping review showed various blood parameter and biomarker increases in COVID-19 patients with periodontitis, encompassing D-dimer, troponin, CRP, pro-brain natriuretic peptide (pro-BNP), procalcitonin, HbA1c, ferritin, and WBC. Periodontal disease-induced inflammation could impose as a procoagulant risk factor which then increases fibrinogen degradation products, including D-dimer (Dikshit 2015). This finding could be associated with COVID-19 severity, considering COVID-19 patients with severe symptoms tend to undergo coagulation function dysregulation and have higher D-dimer levels (Yu *et al.* 2020).

A study conducted by Boyapati *et al.* (2018) also discovered a positive relation between an increase in troponin biomarkers and periodontal parameters such as probing depth and Periodontal Inflammatory Surface Area (PISA). Troponin increase is also often found in COVID-19 patients and is associated with fatal outcomes (Abbasi *et al.* 2020). C-reactive protein (CRP), an acute reactant phase product generated by the heart is also increased in periodontal disease, caused by inflammatory mediators that could stimulate hepatocytes to produce CRP (Bansal *et al.* 2014). In COVID-19 patients with worse symptoms, CRP is also found to increase, thus accordingly this biomarker could be used to monitor and evaluate COVID-19 progress (Sadeghi-Haddad-Zavareh *et al.* 2021). In physiological conditions, procalcitonin (PCT) would escalate when inflammation takes place and has a potential as an inflammatory mediator which plays a part in periodontal inflammation (Selvadurai *et al.* 2019). PCT increase also happens in COVID-19 patients, markedly in severe patients (four times higher) and critical patients (eight times higher) compared to moderate COVID-19 patients (Hu *et al.* 2020).

Periodontopathogens produce lipopolysaccharides which are bound to enter blood circulation, increase adhesion molecules and proinflammatory cytokines release which then causes systemic inflammation and an increase of serum N-terminal-pro-BNP (NT-proBNP) (Leira & Blanco 2018). NT-proBNP is frequently found in COVID-19 patients and is strongly associated with mortality (Caro-Codón *et al.* 2021). Increase of glycosylated hemoglobin (HbA1c) in periodontitis patients could be attributed to periodontopathogens and their products that could stimulate cells to release proinflammatory cytokines and consequently disrupt glucose and lipid metabolism (Rajan *et al.* 2013). HbA1c increase is also associated with COVID-19 prognosis and an increase in COVID-19 mortality in diabetic patients with poor glycaemic control before infection (Prattichizzo *et al.* 2021).

In an acute response phase, TNF-α and IL-1β increase serum ferritin, a systemic inflammation indicator (Gupta *et al.* 2021). According to Thounaojam (2019), ferritin increases in chronic periodontitis patients. Abnormal ferritin levels in COVID-19 patients were associated with higher risk of liver damage and illness, thus ferritin is useful in detecting COVID-19 prognosis (Hussein *et al.* 2021). Increase in white blood cell (WBC) also ensues due to polymorphonuclear cells that play a role as a mediator in periodontal inflammation (Kumar *et al.* 2014). A study conducted by Zhu *et al.* (2021) also showed an association between WBC level with mortality in COVID-19 patients; therefore, this parameter needs to be discerned in handling COVID-19 patients (Zhu *et al.* 2021).

3.2 *Periodontitis in relation to hospitalization, mortality, ICU admission, and ventilation assistance of COVID-19 patients*

Based on the findings presented above, periodontitis increases blood markers correlated with COVID-19 severity (Marouf *et al.* 2021). This scoping review also found an association between periodontitis with COVID-19 hospitalization, ventilation assistance, ICU

admission, and also mortality. However, according to Larvin *et al.* (2020), there was no link between loose teeth indicator and COVID-19 hospitalization based on a cohort depending on self-reported indicators by research subjects. This could be attributed to the small size of the periodontitis subgroup, and the possibility of patients undergoing periodontal treatments, tooth extraction, or self-exfoliated teeth. In addition, there could also be inaccuracy of self-reported indicators by the research subjects. According to Larvin *et al.* (2021), there is also a hospitalization and mortality increase in COVID-19 obese patients compared to those without periodontitis. Obesity and periodontitis have combined or synergistic effects on systemic inflammation which prompts metabolic dysregulation (Jepsen *et al.* 2020). Therefore, it can be concluded that periodontal inflammation and obesity synergistically worsen COVID-19 outcomes (Larvin *et al.* 2021).

3.3 *Hypotheses underlying the relationship between COVID-19 and periodontitis*

Hypotheses regarding the mechanistic link between periodontitis and COVID-19 severity have been proposed. A prior scoping review conducted by Basso *et al.* (2021) reviewed hypotheses underlying the relationship between COVID-19 and periodontal diseases. The studies included in the scoping review mentioned stated that certain molecules (ACE2, furin, cathepsin, and TMPRSS2) increase in periodontitis patients and play a role in SARS-CoV-2 emergence. Periodontopathic bacteria also take part in SARS-CoV-2 entry by cleaving the S protein of SARS-CoV-2 and increasing cytokine production which then contributes to the COVID-19 cytokine storm. Periodontal pockets could also act as a SARS-CoV-2 reservoir, hence gingival epithelial ulceration in periodontitis patients could attribute to a higher risk of SARS-CoV-2 infection. A study by Gupta *et al.* (2021) also found a similarity in Neutrophil Extracellular Traps (NET) that are involved in both COVID-19 and periodontitis pathogenesis (Marouf *et al.* 2021).

4 CONCLUSION

Research methods implemented thus far regarding periodontitis impact in relation to COVID-19 severity are case-control, cohort, cross-sectional, and analytical retrospective studies. Periodontitis substantially aggravates COVID-19 symptoms by escalating D-dimer, troponin, CRP, pro-BNP, procalcitonin, HbA1c, ferritin, and WBC which then increases hospitalization, mortality, ICU admission, and ventilation assistance. Therefore, oral hygiene maintenance is necessary in view of the fact that consequences caused by periodontitis could alter COVID-19 prognosis. Contradictory results in periodontitis effects toward hospitalization impose further research to be done. Further experimental research (*in vitro* and *in vivo*) is necessary to perceive the causal effect between periodontitis and COVID-19. Synergistic effects between periodontitis and other comorbidities are also in need of further research to identify patients who are more prone to unfavorable COVID-19 outcomes.

REFERENCES

Abbasi, B.Al, Torres, P., Ramos-Tuarez, F., Dewaswala, N., Abdallah, A., Chen, K., Qader, M.A., Job, R., Aboulenain, S., Dziadkowiec, K., Bhopalwala, H., Pino, J.E. & Chait, R.D. 2020. Cardiac troponin-I and COVID-19: A prognostic tool for in-hospital mortality. *Cardiology Research* 11(6): 398–404.

Azer, S.A. 2020. COVID-19: pathophysiology, diagnosis, complications and investigational therapeutics. *New Microbes and New Infections* 37: 1–8.

Bansal, T., Pandey, A., Deepa, D. & Asthana, A.K. 2014. C-reactive protein (CRP) and its association with periodontal disease: A brief review. *Journal of Clinical and Diagnostic Research* 8(7): 21–24.

Basso, L., Chacun, D., Sy, K., Grosgogeat, B. & Gritsch, K. 2021. Periodontal diseases and COVID-19: A scoping review. *European Journal of Dentistry* 15(4): 768–775.

Belstrøm, D., Damgaard, C., Könönen, E., Gürsoy, M., Holmstrup, P. & Gürsoy, U.K. 2017. Salivary cytokine levels in early gingival inflammation. *Journal of Oral Microbiology* 9(1): 1–6.

Boyapati, R., Vudathaneni, V., Nadella, S.B., Ramachandran, R., Dhulipalla, R. & Adurty, C. 2018. Mapping the link between cardiac biomarkers and chronic periodontitis: A clinico-biochemical study. *Journal of Indian Society of Periodontology* 24(4): 309–315.

Caro-Codón, J., Rey, J.R., Buño, A., Iniesta, A.M., Rosillo, S.O., Castrejon-Castrejon, S., Rodriguez-Sotelo, L., Martinez, L.A., Marco, I., Merino, C., Martin-Polo, L., Garcia-Veas, J.M., Martinez-Cossiani, M., Gonzalez-Valle, L., Herrero, A., López-de-Sa, E. & Merino, J.L. 2021. Characterization of NT-proBNP in a large cohort of COVID-19 patients. *European Journal of Heart Failure* 23(3): 456–464.

Ciornei, R.T. 2020. Prevention of severe coronavirus disease 2019 outcomes by reducing low-grade inflammation in high-risk categories. *Frontiers in Immunology* 11(1762): 1–5.

Deo, V., Pilania, D., Kumar, P. & Yadav, R. 2021. Angiotensin converting enzyme 2 and inflammatory cytokines: A potential link between chronic periodontitis and COVID-19. *World Journal of Advanced Research and Reviews* 9(1): 062–068.

Dikshit, S. 2015. Fibrinogen degradation products and periodontitis: Deciphering the connection. *Journal of Clinical and Diagnostic Research* 9(12): 10–12.

Fabri, G.M.C. 2020. Potential link between COVID-19 and periodontitis: cytokine storm, immunosuppression, and dysbiosis. *Oral Health and Dental Management* 20(1): 1–5.

Fajnzylber, J., Regan, J., Coxen, K., Corry, H., Wong, C., Rosenthal, A., Worrall, D., Giguel, F., Piechocka-Trocha, A., Atyeo, C., Fischinger, S., Chan, A., Flaherty, K.T., Hall, K., Dougan, M., Ryan, E.T., Gillespie, E., Chishti, R., Li, Y., … Zhu, A. 2020. SARS-CoV-2 viral load is associated with increased disease severity and mortality. *Nature Communications* 11(1): 1–9.

Garcés Villalá, M.A., Nollen, J.A., Rico, S.D., Cortez Quiroga, G.A., Calvo Guirado, J.L. & Aubone De Los Rios, G.O. 2020. COVID 19, pathophysiology and prospects for early detection in patients with mild symptoms of the controversial virus in underdeveloped countries. *Journal of Health Science and Prevention* 4(2): 91–98.

Gupta, S., Mohindra, R., Singla, M., Khera, S., Sahni, V., Kanta, P., Soni, R.K., Kumar, A., Gauba, K., Goyal, K., Singh, M.P., Ghosh, A., Kajal, K., Mahajan, V., Bhalla, A., Sorsa, T. & Räisänen, I. 2021. The clinical association between periodontitis and COVID-19. *Clinical Oral Investigations* 26: 1361–1374.

Hu, R., Han, C., Pei, S., Yin, M. & Chen, X. 2020. Procalcitonin levels in COVID-19 patients. *International Journal of Antimicrobial Agents* 56(2): 106051.

Hussein, A.M., Taha, Z.B., Malek, A.G., Rasul, K.A., Hazim, D.Q., Ahmed, R.J. & Mohamed, U.B. 2021. D-dimer and serum ferritin as an independent risk factor for severity in COVID-19 patients. *Materials Today: Proceedings, 13 April 2021*. Bethesda, Maryland: National Library of Medicine.

Jepsen, S., Suvan, J. & Deschner, J. 2020. The association of periodontal diseases with metabolic syndrome and obesity. *Periodontology 2000* 83(1): 125–153.

Kumar, B.P., Khaitan, T., Ramaswamy, P., Sreenivasulu, P., Uday, G. & Velugubantla, R.G. 2014. Association of chronic periodontitis with white blood cell and platelet count – A case control study. *Journal of Clinical and Experimental Dentistry* 6(3): 214–217.

Larvin, H., Wilmott, S., Kang, J., Aggarwal, V.R., Pavitt, S. & Wu, J. 2021. Additive Effect of periodontal disease and obesity on COVID-19 outcomes. *Journal of Dental Research* 100(11): 1228–1235.

Larvin, H., Wilmott, S., Wu, J. & Kang, J. 2020. The impact of periodontal disease on hospital admission and mortality during COVID-19 pandemic. *Frontiers in Medicine* 7(604980): 1–7.

Leira, Y. & Blanco, J. 2018. Brain natriuretic peptide serum levels in periodontitis. *Journal of Periodontal Research* 53(4): 575–581.

Marouf, N., Cai, W., Said, K.N., Daas, H., Diab, H., Chinta, V.R., Hssain, A.A., Nicolau, B., Sanz, M. & Tamimi, F. 2021. Association between periodontitis and severity of COVID-19 infection: A case-control study. *Journal of Clinical Periodontology* 48(4): 483–491.

Martu, M.-A., Maftei, G.G.-A., Sufaru, I.-G., Jelihovschi, I., Luchian, I., Hurjui, L., Martu, I. & Pasarin, L. 2020. COVID-19 and periodontal disease—Ethiopathogenic and clinical implications. *Rom. J. Oral Rehabil* 12(4): 116–124.

Marzano, A.V., Genovese, G., Moltrasio, C., Gaspari, V., Vezzoli, P., Maione, V., Misciali, C., Sena, P., Patrizi, A., Offidani, A., Quaglino, P., Arco, R., Caproni, M., Rovesti, M., Bordin, G., Recalcati, S., Potenza, C., Guarneri, C., Fabbrocini, G., … Berti, E. 2021. The clinical spectrum of COVID-19–associated cutaneous manifestations: An Italian multicenter study of 200 adult patients. *Journal of the American Academy of Dermatology* 84(5): 1356–1363.

National Health Commission & National Administration of Traditional Chinese Medicine. 2020. Diagnosis and treatment protocol for novel coronavirus pneumonia (Trial version 7). *Chinese Medical Journal* 133(9): 1087–1095.

Nazir, M.A. 2017. Prevalence of periodontal disease, its association with systemic diseases and prevention. *International Journal of Health Sciences* 1(2): 72–80.

Prattichizzo, F., de Candia, P., Nicolucci, A. & Ceriello, A. 2021. Elevated HbA1c levels in pre-Covid-19 infection increases the risk of mortality: A sistematic review and meta-analysis. *Diabetes/Metabolism Research and Reviews* 2021(e3476): 1–8.

Rajan, P., Nera, M., Pavalura, A.K., Medandrao, N. & Kumar, S.C. 2013. Comparison of glycosylated hemoglobin (HbA1C) levels in patients with chronic periodontitis and healthy controls. *Dental Research Journal* 10(3): 389–393.

Sadeghi-Haddad-Zavareh, M., Bayani, M., Shokri, M., Ebrahimpour, S., Babazadeh, A., Mehraeen, R., Moudi, E., Rostami, A., Barary, M., Hosseini, A., Bijani, A. & Javanian, M. 2021. C-reactive protein as a prognostic indicator in COVID-19 patients. *Interdisciplinary Perspectives on Infectious Diseases* 2021: 1–5.

Selvadurai, K., Varadhan, K.B. & Venkatesh, P.M. 2019. Effects of non-surgical periodontal therapy on procalcitonin levels of gingival crevicular fluid and serum in subjects with different periodontal conditions. *Journal of the International Academy of Periodontology* 21(3): 111–117.

Shaw, L., Harjunmaa, U., Doyle, R., Mulewa, S., Charlie, D., Maleta, K., Callard, R., Sarah Walker, A., Balloux, F., Ashorn, P. & Klein, N. 2016. Distinguishing the signals of gingivitis and periodontitis in supragingival plaque: A cross-sectional cohort study in Malawi. *Applied and Environmental Microbiology* 82(19): 6057–6067.

Sirin, D.A. & Ozcelik, F. 2021. The relationship between COVID-19 and the dental damage stage determined by radiological examination. *Oral Radiology* 37(4): 600–609.

Soy, M., Keser, G., Atagündüz, P., Tabak, F., Atagündüz, I. & Kayhan, S. 2020. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. *Clinical Rheumatology* 39(7): 2085–2094.

Sukumar, K. & Tadepalli, A. 2021. Nexus between COVID-19 and periodontal disease. *Journal of International Medical Research* 49(3): 1–11.

Takahashi, Y., Watanabe, N., Kamio, N., Kobayashi, R., Iinuma, T. & Imai, K. 2021a. Aspiration of periodontopathic bacteria due to poor oral hygiene potentially contributes to the aggravation of COVID-19. *Journal of Oral Science* 63(1): 1–3.

Takahashi, Y., Watanabe, N., Kamio, N., Yokoe, S., Suzuki, R., Sato, S., Iinuma, T. & Imai, K. 2021b. Expression of the SARS-CoV-2 receptor ACE2 and proinflammatory cytokines induced by the periodontopathic bacterium fusobacterium nucleatum in human respiratory epithelial cells. *International Journal of Molecular Sciences* 22(1352): 1–13.

Thounaojam, N. 2019. Effects of chronic periodontitis in serum ferritin levels before and 1 month after non-surgical periodontal therapy: An intervention study. *International Journal of Preventive and Clinical Dental Research* 6(2): 32.

Wang, Y., Deng, H., Pan, Y., Lin, L., Hu, R., Lu, Y., Deng, W., Sun, W., Shen, X. & Huang, X.-F. 2021. *Periodontal disease increases the host susceptibility to COVID-19 and its severity: A Mendelian randomization study*. *Journal of Translational Medicine* 19: 1–9.

Yu, H.H., Qin, C., Chen, M., Wang, W. & Tian, D.S. 2020. D-dimer level is associated with the severity of COVID-19. *Thrombosis Research* 195(2020): 219–225.

Yuki, K., Fujiogi, M. & Koutsogiannaki, S. 2020. COVID-19 pathophysiology: A review. *Clinical Immunology* 215(108427): 1–7.

Zhu, B., Feng, X., Jiang, C., Mi, S., Yang, L., Zhao, Z., Zhang, Y. & Zhang, L. 2021. Correlation between white blood cell count at admission and mortality in COVID-19 patients: A retrospective study. *BMC Infectious Diseases* 21(1): 1–5.

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by Sophie Ailsa

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Periodontitis Effects Toward the Extent of COVID-19 Severity (Scoping Review)

Sophie Ailsa Arthur
Faculty of Dentistry, Trisakti University, Indonesia

Ing. Marie Louisa, Sp. Perio
Department of Periodontology, Faculty of Dentistry, Trisakti University

ABSTRACT:

Background(s):

In December 2019, SARS-CoV-2 started spreading in China, subsequently causing worldwide COVID-19 pandemic which affects various organs, predominantly respiration. Periodontitis, a chronic inflammation disease of periodontal tissues, also alters our systemic immune response. Consequently, periodontitis is presumed to play a part in COVID-19 severity.

Objective(s)

This research was conducted to ascertain different research methods implemented to determine periodontitis effects towards COVID-19 severity, and also blood parameters, biomarkers, and COVID-19 severity parameters which were significantly contrasting in COVID-19 patients with periodontitis.

Method(s):

This scoping review was carried out utilizing PRISMA diagram consisting of literature associated with COVID-19 patients as population, periodontitis impact towards COVID-19 severity as concept, and global as context in several databases, that are PubMed, WILEY, and Google Scholar.

Main finding(s):

Five journals in line with inclusion criteria applied confirmed various affiliation between periodontitis and COVID-19 severity. Journals included were one cross sectional study, two cohorts, one case control, and one analytical retrospective study. These studies stated that COVID-19 severity was predicated on several parameters, including blood parameters, biomarkers, hospitalization, mortality, ICU support, and ventilation assistance.

Conclusion(s):

Research methods implemented on periodontitis effects towards COVID-19 severity were case control, cohort, cross sectional, and analytical retrospective study. Periodontitis aggravates COVID-19 severity as a result of increased parameters (D-dimer, troponin, CRP, pro-BNP, procalcitonin, HbA1c, ferritin, and WBC), consequently increasing hospitalization rate, mortality, ICU support, and ventilation assistance.

Keywords:

Biomarkers, COVID-19 severity, periodontitis

BACKGROUND

In December 2019, a sequence of respiratory diseases dispersed in Wuhan, China that gave rise to Coronavirus disease 2019 (COVID-19) which was then set as a pandemic by World Health Organization (WHO).[1,2] The cause of this disease, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) gains entrance into host cells through the binding of spike protein and angiotensin converting enzyme 2 (ACE2) which are found on cardiac, renal, intestinal, endothelial cells, and alveolar type II cell surfaces.[2,3] Virus mainly enters through lung and spreads towards other organs by means of blood circulation, which could cause organ dysfunction and death.[4] COVID-19 major manifestations include fever, fatigue, and dry cough.[5] Based on its clinical manifestation, COVID-19 cases are divided into asymptomatic, mild, moderate, severe, and critical cases. Critical cases are indicated by the presence of respiratory failure, assisted ventilation, shock, and organ failures that necessitates ICU admission.[5,6]

Periodontal disease is a chronic inflammatory disease of periodontium, and acts as the main reason underlying tooth loss with a prevalence constituting 20-50% of global population.[7] Two main periodontal diseases are gingivitis and periodontitis.[8] Gingivitis (gingival inflammation response) otherwise healed could progress into periodontitis which imposes degradation of periodontal tissue.[9] Besides the local effect generated, periodontitis also increases C-reactive protein (CRP), acute phase proteins, plasma antibody levels, coagulation factors, white blood cell (WBC), and proinflammatory cytokines (interleukin / IL-1β, IL-2, IL-6, Interferon / IFN - γ, and tumor necrosis factor / TNF- α).[10]

There are a lot of various biological possibilities that underlies the association between these two diseases. There is a similar inflammatory pathway between COVID-19 and periodontitis, which is shown by increase of proinflammatory cytokines (IL-1β, IL-2, IL-6, TNF- α, IFN-γ), CRP, acute phase proteins, and coagulation factors.[10] COVID-19 induced cytokine storm is comparable to cytokine imbalance manifested in periodontitis, thus there is a potential relationship between periodontitis and COVID-19 complications.[11]

ACE (main receptors for SARS-CoV-2) are also found in the oral epithelial cells, such as the tongue, buccal mucosa, gingival tissue, periodontal pockets, and gingival crevices.[12] Periodontal pockets could also be an advantageous setting for SARS-CoV-2 replication and survival.[13] Binding between SARS-CoV-2 and ACE2 serves as a cellular entrance that facilitates virus entry and increases viral load in the tissue.[14] Plasma viral load increase is significantly linked with the increase of inflammatory markers and COVID-19 severity.[15] Pneumonia is also one of poor COVID-19 severity indicator.[1] Periodontopathic bacteria are also found in bronchoalveolar lavage fluid (BALF) of pneumonia patients. An increase of periodontopathic bacteria could intensify COVID-19 severity through several mechanisms, involving increase of ACE2 expression, proinflammatory cytokines increase in lower respiratory tract, and periodontopathic bacteria proteases that could facilitate SARS-CoV-2 infection by degrading S protein in SARS-CoV-2.[16]

Several associations pertaining to periodontitis that may potentially increase COVID-19 severity stated above urges the writer's interest in conducting a scoping review based on periodontitis impact towards COVID-19 severity. The objective of this study is to see various methods done on this topic, as well as blood parameters, biomarkers and COVID-19 severity parameters which were remarkably distinct in COVID-19 patients with periodontitis. This study aspires to be an educational means for both professional health workers and general public, and al-

so help to identify individual with more vulnerable risk of COVID-19 severity.

METHOD

This research is done using scoping review method by means of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram. Literature search is done by one researcher between August and December 2021. Search strategy is done by using population, concept, and context criteria, and inclusion and exclusion criteria by using boolean search on three databases as listed in Table 1. Search results on threedatabases obtained as much as 698 journals (31 journals from PubMed, 32 journals from WILEY, and 635 journals from Google Scholar). Out of a number of 698 journals, 46 duplicates were discovered, leaving 652 journals which were then further sorted and assesed based on their title and abstract. A sum of 647 articles were excluded, on the account of 64 articles did not have any association with periodontitis, 31 articles did not have any association with COVID-19 severity, 395 articles did not have both association with periodontitis and COVID-19 severity, 12 journals could not be accessed, 23 articles were response articles, 46 articles were written in languanges apart from Indonesian and English, 24 weren't an article/journal (website, posters, magazines, and so forth), 43 were reviews, and nine article didn't contain any clinical data. Through full-text reading of five articles, no additional articles were excluded.

Table 1. Search strategy

Search Strategy
PCC Criteria : -Population : literature associated with COVID-19 patients -Concept : periodontitis impact towards COVID-19 severity -Context : global
Electronic database : Google Scholar, PubMed, WILEY
Inclusion criteria : Original articles obtained from PubMed, Google Scholar, and WILEY; cohorts, case controls, case reports, cross sectionals, randomized controlled trials, journals and grey literature written in English and Indonesian, journals published since 2020
Exclusion criteria : Response articles, systematical reviews, journals and grey literature written in languages aside from English and Indonesian
Boolean search : ("Periodontal disease" OR "Periodontal manifestation" OR periodontitis) AND ("COVID-19 severity" OR "COVID-19 complications" OR "COVID-19 outcomes" OR "COVID-19 aggravation" OR "COVID-19 disease" OR "COVID-19 exacerbation" OR "worsen COVID-19")

MAIN FINDINGS

The research concludes with five full-text journals acquired and used in this research. The PRISMA diagram denotes the flow of searching and sorting phase, which is displayed in Figure 1. Table 2 represents relevant findings taken from each study.

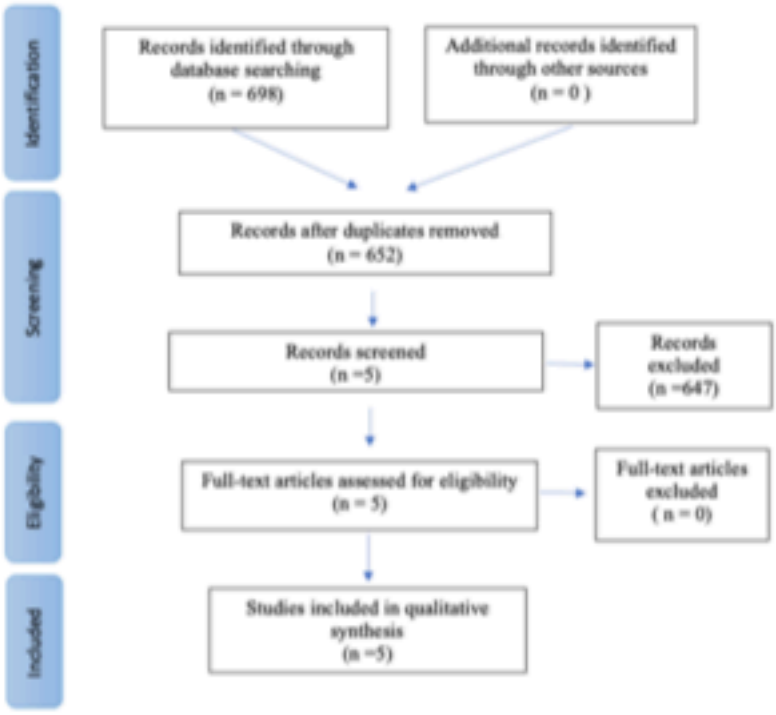

Figure 1. Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA)

Table 2. Extraction table

Authors	Year	Title	Objectives	Sample Group	Study design	Research Result
Gupta S, et al.	2021	The Clinical Association Between Periodontitis and COVID-19.	Association between periodontitis and COVID-19 clinical symptoms	82 COVID-19 positive patients	Cross sectional	Periodontitis impact both direct and indirect towards worse prognosis of COVID-19
Larvin H, et al.	2021	Additive Effect of Periodontal Dis-	Additive effects of periodontal	58.897 datas obtained from UK	Cohort	Periodontal disease could worsen obesity

		ease and Obesity on COVID-19 Outcomes.	disease and obesity towards COVID-19	Biobank cohort study between March 2020 and February 2021		effect towards COVID-19 hospitalization and mortality
Larvin H, et al.	2020	The Impact of Periodontal Disease on Hospital Admission and Mortality During COVID-19 Pandemic.	To ascertain periodontal disease impact towards COVID-19 patients' hospitalization and mortality	13,253 data obtained from UK Biobank cohort study between March and June 2020	Cohort	No heightened risk of mortality and hospitalization of COVID-19 patients with loose teeth as an indicator of periodontal disease
Maruf N, et al.	2021	Association Between Periodontitis and Severity of COVID-19 Infection: A Case-Control Study.	Association between periodontitis and COVID-19 complications	Electronic health data of 568 COVID-19 patients with active dental records	Case control	Association between periodontitis and elevated risk of COVID-19 complications (ICU admission, need for assisted ventilation, death, and biomarker elevation)
Sirin DA, et al.	2021	The Relationship Between COVID-19 and the Dental Damage Stage Determined by Radiological Examination.	Link between dental damage stage and COVID-19 severity	Dental Damage Stage data based upon Apical Periodontitis Grading Scale, Radiologic Alveolar Bone Loss and Pathophysiological Process of Dental Caries from 137 COVID-19 positive patients	Analytical retrospective	Connection observed between dental damage stage and COVID-19 severity that is fit for extensive studies

Datas obtained from full-text journals used in this study is then divided and categorized into several different categories which are displayed in different tables. Categories related to COVID-19 severity are divided into blood parameters and biomarkers, hospitalization, mortality, assisted ventilation, and ICU admission.

Two articles mentioned periodontitis impact towards blood parameters and biomarkers which

modifies COVID-19 severity (Table 3). Research conducted by Gupta et al. stated that patients with periodontitis have higher levels of CRP, D-dimer, HbA1c, ferritin, troponin, pro-BNP, and procalcitonin.[17] At the same time, Marouf et al. claimed that heightened levels of HbA1c, WBC, and CRP are seen in COVID-19 patients with periodontitis.[18]

Association between periodontitis and the risk of COVID-19 hospitalization is shown on four articles (Table 4). A study conducted by Gupta et al. shows a heightened risk of hospitalization on patients with periodontitis.[17] Table 4 mentions two separate researches carried out by Larvin et al., where both articles utilizes data extracted from UK Biobank cohort study which uses self-reported indicators by patients with bleeding and painful gums (mild to moderate periodontal disease indicator) and loose teeth (severe periodontal disease indicator).[19,20]

Table 3. Blood parameters and biomarkers

Authors	Sample group	Research results
Gupta S, et al.	82 COVID-19 positive patients (27 patients without periodontal disease, 21 patients with gingivitis, and 34 patients with stage I-IV periodontitis)	1. Gingival recession and missing teeth on account of periodontal disease was related to D-dimer and troponin levels. 2. Significant association between probing depth and levels of HbA1c, CRP, D-dimer, and ferritin. 3. Higher clinical attachment loss (CAL) was connected to heightened levels of CRP, D-dimer, pro-BNP, troponin, and procalcitonin levels. 4. Patients with higher degree of periodontitis severity have heightened D-dimer, pro-BNP, and troponin levels.
Marouf N, et al.	Electronic health data of 568 COVID-19 positive patients (258 patients with periodontitis)	Higher HbA1c, WBC, CRP levels in COVID-19 patients with periodontitis compared to those without.

Table 4. Hospitalization

Authors	Sample group	Research results
Gupta S, et al.	82 COVID-19 positive patients (27 patients without periodontal disease, 21 patients with gingivitis, and 34 patients with stage I-IV periodontitis)	COVID-19 patients with periodontitis had higher risk of hospitalization.
Larvin H, et al.	58.897 datas obtained from UK Biobank cohort study between March 2020 and February 2021 (14.466 positive COVID-19 cases, encompassing 6.124 patients with bleeding gums, 1.511 patients with loose teeth, 1.397 patients with painful gums, and 49.565 patients without any history of periodontal disease)	Obese COVID-19 patients with periodontal disease had higher chance of hospitalization compared obese COVID-19 patients without any periodontal disease.
Larvin	13.253 datas obtained from UK Biobank	Loose teeth as a periodontal

H, et al.	cohort study between March and June 2020 (365 patients with painful gums, 1.329 patients with bleeding gums, 406 patients with loose teeth, and 11.153 patients without any history of periodontal disease)	disease indicator wasn't associated with higher COVID-19 hospitalization.
Sirin DA, et al.	Dental Damage Stage (DD Stg) data based upon Apical Periodontitis Grading Scale, Radiologic Alveolar Bone Loss dan Pathophysiological Process of Dental Caries from 137 COVID-19 positive patients	Patients expressing Dental Damage Stage (DD Stg) 2 and 3 had higher COVID-19 hospitalization in comparison to patients with DD Stg 0 and 1.

'Additive Effect of Periodontal Disease and Obesity on COVID-19 Outcomes' which studies 58.897 datas between March 2020 and February 2021 showed an increase of hospitalization in obese COVID-19 patients with periodontal disease indicator compared those without, which proves an evident additive effect between periodontal disease and obesity which exerts influence on COVID-19 severity.[20] However, contradictory to the journal previously mentioned, 'The impact of periodontal disease on hospital admission and mortality during COVID-19 pandemic' which utilized 13.253 datas between March and June 2020 showed no association between loose teeth indicator with COVID-19 hospitalization.[19]

One study done by Sirin et al. explores the relation of COVID-19 severity with DD Stg (dental status indicator based on the summation of APGS, RBL and PPDC scores which are then further categorized into four classification, which are DD Stg 0 (healthy), DD Stg 1 (mild), DD Stg 2 (moderate) dan DD Stg 3 (severe). Study result shows that patients with DD Stg 2 and 3 exhibited higher hospitalization in contrast with patients with DD Stg 0 and 1.[21]

Table 5 discusses the association between periodontitis and mortality of COVID-19 patients. A study conducted by Gupta et al and Marouf et al conveys that periodontitis increases mortality rate in COVID-19 patients.[17,18] Corresponding to this discovery, another study conducted by Sirin et al found that patients with DD Stg 3 notably had higher mortality rate compared to lower DD Stg.[21]

Another study conducted by Larvin et al in 'Additive Effect of Periodontal Disease and Obesity on COVID-19 Outcomes' showed increased mortality risk in obese COVID-19 patients with periodontitis.[20] Dissimilar to this finding, a different study conducted by Larvin et al. in 'The impact of periodontal disease on hospital admission and mortality during COVID-19 pandemic' using different sample groups stated no association between loose teeth as a periodontal disease indicator with mortality rate in COVID-19 patients.[19]

Based on Table 6, studies done by Gupta et al. and Marouf et al. showed a relation between periodontitis with the need of assisted ventilation.[17,18] This finding indicates that periodontitis is related with higher COVID-19 severity, owing to the fact that the need of ventilation assistance is a poorer COVID-19 severity indicator.[5]

Table 7 shows data from two studies conducted by Gupta et al. and Marouf et al., where both studies presented that periodontitis affects COVID-19 patients ICU admission.[17,18] Both studies connects periodontitis with COVID-19 severity, in view of the fact that ICU admission is considered one of unfavorable COVID-19 severity indication.[5]

Table 5. Mortality

Authors	Sample group	Research results
Gupta S, et al.	82 COVID-19 positive patients (27 patients without periodontal disease, 21 patients with gingivitis, and 34 patients with stage I-IV periodontitis)	Patients with mortality had a greater degree of periodontitis severity.
Larvin H, et al.	58.897 datas obtained from UK Biobank cohort study between March 2020 and February 2021 (14.466 positive COVID-19 cases, encompassing 6.124 patients experiencing bleeding gums, 1.511 patients experiencing loose teeth, 1.397 patients experiencing painful gums, and 49.565 patients without any history of periodontal disease)	Obese COVID-19 patients with periodontal disease had higher rates of mortality compared to obese COVID-19 patients without periodontal disease.
Larvin H, et al.	13.253 datas obtained from UK Biobank cohort study between March and June 2020 (365 patients experiencing painful gums, 1.329 patients experiencing bleeding gums, 406 patients experiencing loose teeth, and 11.153 patients without any history of periodontal disease)	Loose teeth as a periodontal disease indicator did not have any relation with increase of mortality rate in COVID-19.
Marouf N, et al.	Electronic health data of 568 COVID-19 positive patients (258 patients with periodontitis)	Periodontitis was connected with an increased risk of mortality in COVID-19 patients.
Sirin DA, et al.	Dental Damage Stage data based upon APGS, RBL and PPDC scores obtained from 137 COVID-19 positive patients	Patients with DD Stg 3 had a significant increase of mortality rate.

Table 6. Assisted ventilation

Authors	Sample group	Research results
Gupta S, et al.	82 COVID-19 positive patients (27 patients without periodontal disease, 21 patients with gingivitis, and 34 patients with stage I-IV periodontitis)	Significant association between BOP, probing depth, gingival recession, CAL with oxygen requirement and assisted ventilation in COVID-19 patients, particularly in patients exhibiting stage III and IV periodontitis.
Marouf N, et al.	Electronic health data of 568 COVID-19 positive patients (258 patients with periodontitis)	Association between periodontitis and the need of assisted ventilation.

Table 7. ICU admission

Authors	Sample group	Research results
Gupta S, et al.	82 COVID-19 positive patients (27 patients without periodontal disease, 21 patients with gingivitis, and 34 patients with stage I-IV periodontitis)	COVID-19 patients with higher severity of periodontitis underwent ICU admission in contrast to those with healthy periodontal tissues which generally only encounter home isolation or ward admission.
Marouf	Electronic health data of 568 COVID-	Periodontitis had a significant impact

N, et al.	19 positive patients (258 patients with periodontitis)	towards the need of assisted ventilation in COVID-19 patients.

Previous studies stated above have proven to validate the associations between periodontitis and COVID-19 severity. An earlier study conducted by Marouf et al. (2021) showed an association between periodontitis and higher mortality, especially if there are comorbidities involved.[18] A Mendelian randomization study carried out by Wang et al. (2021) also discovered significant association between genetically proxied periodontal disease with heightened risk of COVID-19 susceptibility and hospitalization.[22] A study conducted by Takahashi et al. (2021) also found culture supernatant *Fusobacterium nucleatum* (CSF) effect on the increase of ACE2 expression, IL-6, and IL-8 on COVID-19 patients. This finding reinforces the hypothesis stating that periodontopathic bacteria increase can cause poorer COVID-19 severity.[23]

Periodontitis effects towards biomarkers in COVID-19 patients

Out of 698 journals, 46 duplicates were discovered and furthermore 647 journals were excluded, leaving five full-text articles deemed relevant. Five articles mentioned used various research methods, consisting one cross sectional, two cohorts, one case control, and one analytical retrospective study. This scoping review showed various blood parameter and biomarker increase in COVID-19 patients with periodontitis, encompassing D-dimer, troponin, CRP, pro-brain natriuretic peptide (pro-BNP), procalcitonin, HbA1c, ferritin, and WBC. Periodontal disease induced inflammation could impose as a procoagulant risk factor which then increases fibrinogen degradation products, including D-dimer.[24] This finding could be associated to COVID-19 severity, considering COVID-19 patients with severe symptoms tend to undergo coagulation function disregulation and have higher D-dimer levels.[25]

A study conducted by Boyapati et al. (2018) also discovered a positive relation between an increase in troponin biomarker and periodontal parameters such as probing depth and Periodontal Inflammatory Surface Area (PISA).[26] Troponin increase is also often found in COVID-19 patients and associated with fatal outcomes.[27] C-reactive protein (CRP), an acute reactant phase product generated by the heart is also increased in periodontal disease, caused by inflammatory mediators that could stimulate hepatocytes to produce CRP.[28] In COVID-19 patients with worse symptoms, CRP is also found increased, thus accordingly this biomarker could be used to monitor and evaluate COVID-19 progress.[29] In physiological conditions, procalcitonin (PCT) would escalate when inflammation takes place, and has a potential as an inflammatory mediator which plays a part in periodontal inflammation.[30] PCT increase also happens in COVID-19 patients, markedly in severe patients (four times higher) and critical patients (eight times higher) compared to moderate COVID-19 patients.[31]

Periodontopathogens produce lipopolysaccharides which are bound to enter blood circulation, increase adhesion molecules and proinflammatory cytokines release which then causes systemic inflammation and an increase of serum N-terminal-pro-BNP (NT-proBNP).[32] NT-proBNP is frequenly found in COVID-19 patients and strongly associated with mortality.[33] Increase of glycosylated hemoglobin (HbA1c) in periodontitis patients could be attributed to periodontopathogens and their products that could stimulate cells to release proinflammatory cytokines and consequently disrupt glucose and lipid metabolism.[34] HbA1c increase is also

associated with COVID-19 prognosis and an increase in COVID-19 mortality in diabetic patients with poor glycaemic control before infection.[35]

In an acute response phase, TNF-α and IL-1β increases serum ferritin, a systemic inflammation indicator.[17] According to Thounaojam (2019), ferritin increases in chronic periodontitis patients.[36] Abnormal ferritin levels in COVID-19 patients were associated with higher risk of liver damage and illness, thus ferritin is useful in detecting COVID-19 prognosis.[37] White blood cells (WBC) increase also ensue due to polymorphonuclear cells that play a role as a mediator in periodontal inflammation.[38] Study conducted by Zhu et al. (2021) also showed association between WBC level with mortality in COVID-19 patients, therefore this parameter need to be discerned in handling COVID-19 patients.[39]

Periodontitis in relation with hospitalization, mortality, ICU admission, and ventilation assistance of COVID-19 patients

Based on the findings presented above, periodontitis increases blood markers correlated with COVID-19 severity.[18] This scoping review also found association between periodontitis with COVID-19 hospitalization, ventilation assistance, ICU admission, and also mortality. However, according to Larvin et al. (2020) there was no link between loose teeth indicator and COVID-19 hospitalization based on a cohort depending on self-reported indicators by research subjects. This could be attributed to the small size of periodontitis subgroup, the possibility of patients undergone periodontal treatments, tooth extraction, or self-exfoliated teeth. [19] In addition, there could also be inaccuracy of self-reported indicators by the research subjects. According to Larvin et al. (2021), there is also a hospitalization and mortality increase in COVID-19 obese patients compared to those without periodontitis.[20] Obesity and periodontitis have combined or synergistic effect on systemic inflammation which prompts metabolic disregulation.[40] Therefore, it can be concluded that periodontal inflammation and obesity sinergestically worsen COVID-19 outcomes.[20]

Hypotheses underlying the relationship between COVID-19 and periodontitis

Hypotheses regarding mechanistic link between periodontitis and COVID-19 severity have been proposed. A prior scoping review conducted by Basso et al. (2021) reviewed hypotheses underlying relation between COVID-19 and periodontal diseases.The studies included in the scoping review mentioned stated that certain molecules (ACE2, furin, cathepsin and TMPRSS2) increases in periodontitis patients and play a role in SARS-CoV-2 entry. Periodontopathic bacteria also take part in SARS-CoV-2 entry by cleaving the S protein of SARS-CoV-2 and increases cytokine production which then contributes to COVID-19 cytokine storm. Periodontal pockets could also act as SARS-CoV-2 reservoir, hence gingival epithelial ulceration in periodontitis patients could attribute to higher risk of SARS-CoV-2 infection.[41] A study by Gupta et al (2020) also found the similarity of Neutrophil Extracellular Traps (NET) that are involved in both COVID-19 and periodontitis pathogenesis.[18]

CONCLUSION

Research methods implemented thus far regarding periodontitis impact in relation to COVID-19 severity are case control, cohort, cross sectional, and analytical retrospective study. Periodontitis substantially aggravates COVID-19 symptoms by escalating D-dimer, troponin, CRP, pro-BNP, procalcitonin, HbA1c, ferritin, and WBC which then increases hospitalization, mortality, ICU admission, and ventilation assistance. Therefore, oral hygiene maintenance is necessary in view of the fact that

consequences caused by periodontitis could alter COVID-19 prognosis. Contradictory results in periodontitis effects towards hospitalization imposes further researches to be done. Further experimental researches (in vitro and in vivo) is necessary to perceive the causal effect between periodontitis and COVID-19. Synergistic effects between periodontitis and other comorbidities are also in need of further research to identify patients who are more prone to unfavorable COVID-19 outcomes.

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