Correlation between Periodontal Diseases and COVID-19: Systematic Review and Meta-Analysis

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Abstract

Objective: To finding the correlation of COVID-19 with periodontal status.

Methods: This systematic review and meta-analysis were aimed to overview studies of the relationship between periodontal disease and the severity of COVID-19 (hospitalization). There were nine studies, analyzed in this systematic review (nine reviews and three meta-analyses). The quality assessment of studies was using Newcastle-Ottawa Scale (NOS) and the pooling effect of meta-analysis were using random-effects model.

Results: The NOS scores were Satisfied (5-6 stars) for seven studies, meanwhile good (7 stars) for two studies. The estimated OR was 2.68 (P=0.006). The heterogeneity (I²) was 61%, showed moderate heterogeneity. COVID-19 and severity depended on the host and viral factors that influence the immune response. The surge of cytokines (especially IL-6) was found as an imperative role in the COVID-19 and periodontal diseases. Finally, periodontal diseases were found positively contributed to the severity of COVID-19.

Conclusion: Periodontal diseases were found associated with the severity and mortality of COVID-19. However, further studies are a necessity to generalize in other populations of COVID-19 patients.

Keywords: COVID-19, Immune, Meta-Analysis, Periodontal diseases, Periodontitis

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Introduction

COVID-19 reached a million cases and dozens of death worldwide. This disease has been caused by SARS-CoV-2 through exposure to respiratory fluids that carry the virus.

The comorbidities become the risk factor for COVID-19 severity and mortality. The comorbidities were reported mainly in men, elderly populations (65-70 years), and with smoking habits. Those were such as hypertension, diabetes, cardiovascular disease, and respiratory diseases. This could pose a serious contribution to the prognosis of COVID-19.2–6

The periodontal disease is caused by bacteria pathogens and results in immune proteins aggregate from cytokines and interleukins that enter the bloodstream. Periodontal diseases also become the risk factors for cardiovascular disease, diabetes mellitus, respiratory disease, rheumatoid arthritis, and other systemic conditions.8–11

Oral and dental symptoms associated with COVID-19 consist of: impaired taste, unspecified oral ulceration, desquamation, periodontitis, gingivitis, petechiae, Kawasaki-like disease, and co-infection, candidiasis, etc.12–16 However, those individual studies had not emphasized the causal relationship and biological plausibility.

The purpose of this systematic review was to overview and emphasize the relationship between periodontitis and the severity of COVID-19. This study is expected for further research the relationship between COVID-19 and oral manifestations.

Methods

This Systematic Review was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020.17

Population

Inclusion: patient with severe COVID-19 (hospitalized or were in ICU); Exclusion: Non-COVID-19 patients.

Exposure

The periodontal disease, also known as gum disease, is a set of inflammatory conditions affecting the tissues surrounding the teeth. In its early stage, called gingivitis. In its more serious form, called periodontitis, the gums can pull away from the tooth, bone can be lost, and the teeth may loosen or fall out.

Comparator

Patients was diagnosed with severe COVID-19 without any periodontal diseases.

Outcome

Patients with severe COVID-19 were hospitalized
and requiring supplemental oxygen from moderate to critical illness.

**Eligible Criteria**
The inclusion criteria were: 1) the observational articles estimated the association between the periodontal disease and the incidence of COVID-19; 2) the observational articles examined at the prevalence of periodontal diseases in COVID-19 patients 3) the studies must be published in English. The exclusion criteria were: 1) absence or without periodontal diseases. 2) studies that were literature reviews, comments, case reports, in vitro or laboratory studies, or letters to the editor.

**Study Search and Selection Strategy**
The electronic searching was conducted on the PubMed, Scopus, Google Scholar, and Cochrane databases to identify relevant research. The search keywords were: “Periodontitis”, “Periodontal”, “Gingivitis”, and “Gingiva”; with “COVID-19” and “SARS-CoV-2”. Articles must be in English. At first, duplicate articles were excluded. Subsequently, the title and abstract assessed independently by five authors. Finally, the full text of the originally included articles was evaluated according to the inclusion and exclusion criteria. Throughout the process, the authors reached a consensus from several discussions.

**Data Extraction**
The following elements were extracted from each article: first author’s last name, year of publication, study type, search location, sample size, exposure assessment, periodontal diseases, outcome, and assessment of irrelevant variables. These data were extracted independently by five authors. Any differences of opinion are discussed to get an agreement between reviewers.

**Quality of Assessment**
The Newcastle-Ottawa Scale (NOS) was used to assess the quality of all included studies. The NOS consisted of three categories; Selection, Comparability, and Exposure (case-control studies) or Outcomes (cohort studies). Furthermore, case-control was divided into 9 items, which include the following groups: S1: Definition of the case; S2: Case representation; S3: Control selection; S4: Definition of adequate control; C1: Comparison of cases; C2: Control studies for baseline analysis; E1: Exposure match; E2: Determination of the same method used for cases and controls; E3: Non-response rate. Each item can achieve one score if the study meets the criteria.

Meanwhile, the cohort study consisted of 8 items; S1: Representation of the exposed cohort; S2: Selection from the non-exposed cohort; S3: Certainty of exposure; S4: Indicates S3: Certainty of exposure; S4: Indicates that the desired outcome was not present at the start of the study; C1: Comparison of cohorts based on design or analysis; O1: Outcome examination; O2: Was the duration of follow-up sufficient for the outcome; O3: Adequate follow-up of the cohort.

For a cross-sectional study, this study used NOS in Naafs et al. Furthermore, the items were divided into 7 parts, namely: S1: Sample representation; S2 Selection from the control group; S3 Certainty of exposure (disease); S4 Non-respondents; C1: Comparison of different outcome groups; O1: Outcome examination; O2: Statistical test. Each item would be given a star if it met the criteria.

Study scores were below 5 showed low quality, 5 and 6 represented moderate/satisfied quality, while 7 and 9 indicated good quality. The five authors assessed the quality of the included studies, separately. Differences of opinions among reviewers were discussed to reach an agreement.19

**Data Synthesis and Analysis**
RevMan software (Review Manager, version 5.4) was for meta-analysis. Odds Ratio (OR) was examined to report the results, with 95% CI for the continuous variable. Forest plot, chi-square of homogeneity test and Higgins Index (I^2) were applied to evaluate heterogeneity. Heterogeneity was considered as: none (I^2<25%), low (25%≤I^2 <50%), moderate (25%≤I^2 <75%), or high (I^2≥75%). In the case of heterogeneity (χ^2 >p<0.05 or I^2>50%), the random effect model was preferred.20-26

**Results**
The electronic search found 443 articles which 50 duplicate articles removed. The electronic search found 443 articles which 50 duplicate articles, removed. There were about 325 articles whose titles were neither appropriate nor relevant for this systematic review. Furthermore, 68 full-text articles were accessed and checked for compliance with the eligible criteria.

A total of 9 articles passed the screening for a systematic review, while 3 of them were included in the meta-analysis. Two studies examined radiographs to determine exposure and outcome of periodontal disease. A total of 6 articles were descriptive cross-sectional studies, 3 of which are studies in which exposure and outcome were based on self-reports.

**Study Quality**
All the cross-sectional studies were rated into the Satisfied category. Others, cohort and case-control studies were almost all categorized as Good, except for the study by Katz et al.27 which was categorized
### Table 1 Study Characteristics

<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Location</th>
<th>Study design</th>
<th>Total sample</th>
<th>Exposure and outcome examination</th>
<th>Population characteristic</th>
<th>Periodontal diseases</th>
<th>Result</th>
<th>NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elibol et al.19</td>
<td>Turkey</td>
<td>CS</td>
<td>155</td>
<td>RT PCR examination, then self-reported</td>
<td>Patients in the hospital, plotted as a ‘pandemic hospital’ by the Turkish Ministry of Health</td>
<td>Gingivitis</td>
<td>1.2 % experience gingivitis</td>
<td>Selection: *** Comparability: Outcome: **</td>
</tr>
<tr>
<td>Ali Sirin et al.20</td>
<td>Turkey</td>
<td>CS</td>
<td>137</td>
<td>RT PCR examination, then radiographic examination</td>
<td>Total of 1,516 patients with a positive real time PCR test for COVID-19 whose examination and treatment for COVID-19 was carried out in a hospital</td>
<td>Alveolar bone loss and Periodontitis from DD Stg damage affects hospitalization for COVID-19 (P&lt;0.0001)</td>
<td>Selection: ** Comparability: Outcome: ***</td>
<td>Score: 6 (Satisfied)</td>
</tr>
<tr>
<td>El Kady et al.21</td>
<td>Egypt</td>
<td>CS</td>
<td>58</td>
<td>Self-report Google Form advertised by Facebook</td>
<td>All patients diagnosed with COVID-19, aged over 18 years and treated in the COVID-19 ward from July 2020 to April 2021.</td>
<td>Presence of gingivitis and biofilm</td>
<td>41.6% had biofilm, and 17.4% had gingivitis</td>
<td>Selection: *** Comparability: Outcome: **</td>
</tr>
<tr>
<td>Fidan et al.22</td>
<td>Turkey</td>
<td>CS</td>
<td>74</td>
<td>Patient data, then the mouth was examined</td>
<td>COVID-19 patients who came to the clinic between April 2020 and October 2020</td>
<td>Gingival bleeding</td>
<td>6% have gingival bleeding</td>
<td>Selection: *** Comparability: Outcome: **</td>
</tr>
<tr>
<td>Gupta et al.23</td>
<td>India</td>
<td>CS</td>
<td>33</td>
<td>Data on COVID-19 patients who came to the hospital, oral examination, and GCF examination</td>
<td>Patients who treated to Infectious Disease Ward institution between 1-25 July 2020</td>
<td>Periodontal diseases such as gingival bleeding, gum swelling, and gingival erythema</td>
<td>42% have periodontal diseases</td>
<td>Selection: *** Comparability: Outcome: ***</td>
</tr>
<tr>
<td>Larvin et al.24</td>
<td>UK</td>
<td>C</td>
<td>+ COVID-19 (1616) - COVID-19 (11637)</td>
<td>COVID-19 patient records at the UK Biobank, then self-reported</td>
<td>COVID-19 patients registered in the UK Biobank between March and June 2020</td>
<td>Gingival bleeding and pain, and tooth loss</td>
<td></td>
<td>Selection: *** Comparability: ** Outcome: **</td>
</tr>
</tbody>
</table>

Gingival bleeding and pain had an OR=1.10 (CI=0.72-1.49) for COVID-19 infection. Tooth loss has an OR=1.15 (CI=0.84-1.59) against COVID-19 infection. Gingival bleeding and pain have OR=8.3 (CI=4.29-16.5), C (95.12-94) for hospitalization. Tooth loss has an OR=0.90, (CI=0.84-1.00) for hospitalization. Gingival bleeding and pain have OR=1.71, (CI=0.5-2.72) on mortality. Tooth loss has OR=0.85 (CI=0.92-2.72) to mortality.
as satisfied.

**Meta-Analysis**

Studies in the meta-analysis showed the association, by measuring the Odds Ratio (OR). The association implemented 2 cohort studies and 1 case-control study. Articles that were taken in the meta-analysis process; were involving studies that examine the risk of periodontitis and hospitalization for COVID-19 patients.

Study of Katz et al.\textsuperscript{27} explored the association between vitamin D and both hospitalization and severity of COVID-19. We considered vitamin D correlated to periodontal diseases, consequently this study was included in the meta-analysis.\textsuperscript{28-30}

In this study, the Generic Inverse Variance (GIV) method was utilized. The meta-analysis implemented a random-effects model, based on the adjusted ORs of those three studies. Standard Error (SE) was measured from the Odds Ratio (OR) and Confidence Interval (CI) using formula:

\[
95\% \ CI = \exp \left( \ln(OR) - 1.96 \times \text{SE} [\ln(OR)] \right) \quad \text{to} \quad \exp \left( \ln(OR) + 1.96 \times \text{SE} [\ln(OR)] \right)
\]

\[
\text{SE} = \frac{\text{Upper 95\% CI} - \log (OR)}{1.96}
\]

Analysis from the model demonstrated that the study of Katz et al.\textsuperscript{27} had the largest weight, while the study of Larvin et al.\textsuperscript{25} had the smallest weight. It was also obtained an estimated OR of 2.68 (P=0.006). This meta-analysis subsequently found that the three studies had 61%, represented moderate heterogeneity.

**Discussion**

Theoretically, the relationship between severity of COVID-19 and periodontal diseases has still uncleared.\textsuperscript{31} However, the relationship between periodontal diseases and comorbidities, has widely reported.\textsuperscript{32-37}

Chronic systemic disease or comorbidity had increased the risk by 6 times for COVID-19 patients to hospitalized. Some author also reported the association between pneumonia and periodontal diseases.\textsuperscript{10,31,38-42} COVID-19 and related severity would influence the immune response. Approximately 80% of patients with COVID-19 have mild symptoms, 20% progress to a severe form of infection associated with higher levels of inflammatory markers such as IL-2, IL-6, IL-10 along with bacterial and neutrophil to lymphocytes counts.\textsuperscript{43}

The surge of cytokines including IL-6, releasing from host cells; referred as the cytokine storm. The cytokine storm has been an important role in disease progression, and biomarker. Similarly, host response of bacterial invasion that caused periodontal diseases and the surge of cytokine. Both of conditions was reported associating with disease progression in COVID-19 patients (especially with comorbidities).
Mainly, the descriptive studies in this systematic review found the presence of periodontal diseases in COVID-19 patients. Furthermore, a study conducted by Larvin et al. reported that patients with periodontal diseases had the protective effect (OR < 1). Conversely, the study also demonstrated bleeding and gum pain and missing teeth with ORs of 1.71 and 1.85 for mortality. This study was based on self-reported, which made it difficult to examine the causal relationship.

The study of Marouf et al. was a case-control design and had a larger OR with a smaller sample study. Increased number of ORs range (CI = 1.39-9.02), assumed a high variation in the study results. However, this study used exposure measurement which is the gold standard in determining the diagnosis of periodontitis (radiograph). These findings were similar to those of Ali Sirin et al. Additionally, Larvin et al.; and Marouf et al. also found a large OR associated with periodontal diseases with mortality. (OR = 8.81, 95%; CI = 1.00-77.7). These findings were consistent with vitamin D deficiency and periodontal diseases had increased the risk of COVID-19 severity and hospitalization (OR=3.64; P < 0.001).

Our study strongly suggested that COVID-19 patients should receive more attention for their periodontal tissue conditions, and prevent the death among patients.

**Conclusion**

Periodontal diseases had been found associated with the severity and mortality of COVID-19, even though further analytics studies are needed to generalize to other populations COVID-19 patients, in order to get more attention for their periodontal tissue conditions, and prevent the death among patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>Non-Severe COVID-19</th>
<th>Severe COVID-19</th>
<th>Total</th>
<th>Bivariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larvin et al.</td>
<td>Non Periodontal</td>
<td>673</td>
<td>665</td>
<td>1338</td>
<td>0.99(0.13-3.02)</td>
</tr>
<tr>
<td></td>
<td>Disease</td>
<td></td>
<td></td>
<td>p&lt;0.005</td>
<td>COVID-19 Severity</td>
</tr>
<tr>
<td></td>
<td>Periodontal</td>
<td>126</td>
<td>99</td>
<td>215</td>
<td>0.91(0.12-2.94)</td>
</tr>
<tr>
<td>Marouf et al.</td>
<td>Non Periodontal</td>
<td>303</td>
<td>7</td>
<td>310</td>
<td>5.57 (2.40-12.9)</td>
</tr>
<tr>
<td></td>
<td>Disease</td>
<td></td>
<td></td>
<td>P=0.003</td>
<td>COVID-19 Severity</td>
</tr>
<tr>
<td></td>
<td>Periodontal</td>
<td>225</td>
<td>29</td>
<td>254</td>
<td>3.54 (1.39-9.05)</td>
</tr>
<tr>
<td>Katz et al.</td>
<td>Non Periodontal</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Disease</td>
<td></td>
<td></td>
<td></td>
<td>COVID-19 Severity</td>
</tr>
</tbody>
</table>

**Figure 2** Pooled Effect from Periodontal Diseases and Severity COVID-19
Acknowledgment

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Conflict of Interest

The authors report no conflict of interest.

References
