Original Research Article

The Impact of Oral Health Status on COVID-19 Severity: A Systematic Literature Review of 25 Studies

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Abstract: **Objectives:** Several risk factors have been recognized in the progress of coronavirus disease 2019 (COVID-19) toward a severe stage. Poor oral health has been relevant to many systemic diseases due to higher inflammation. This study sought to aim the influence of oral health status on severe COVID-19. **Methods:** A systematic search of the medical literature was done using a combination of search terms of online databases including PubMed/Medline, Medline, SCOPUS, Ovid, Cochrane database, and Google Scholar from December 1st, 2019 to July 30th, 2021. Only articles written in the English language were selected. **Results:** A total of 352 studies were reviewed for relevance, specified by the title, abstract, and full copy leading to a yield of 25 articles satisfying inclusion criteria. COVID-19 patients with poor oral health status were at a higher risk of intensive care unit (ICU) hospitalization, need for mechanical ventilation, first and second-week deterioration, delayed recovery period, and mortality. Predisposing individuals to serious systemic diseases, conducting pathogens to the lower airways, developing bacterial co-infection, impairing the function of the innate immune system, increasing expression of angiotensin-converting enzyme-II (ACEII) receptors, and enhancing expression of inflammatory cytokines are oral-related risk factors for severe COVID-19 infection. **Conclusions:** This systematic literature review presents that poor oral health status is linked to severe COVID-19 complications. Monitoring and maintaining oral health, identifying risk groups, and developing appropriate recommendations are simple strategies to combat the current coronavirus crisis.
Keywords: Coronavirus, COVID-19, Oral Health, Oral Hygiene, Periodontal Disease, SARS-Cov-2, Severe.

INTRODUCTION

Oral health as a part of overall health has an essential role in the quality of life [1]. According to the World Health Organization (WHO) definition, oral health is a disease- and disorder-free condition in which an individual's ability to bite, chew, smile, and speak and their psychosocial status are restricted [2]. Hence, an individual's growth and development, psychic, productive, and social capacity can be affected by oral diseases [1].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a newly recognized virus from the coronavirus family that was deemed a worldwide pandemic by WHO in March 2020 [3].

Several risk factors have been determined recognized in the advancement of COVID-19 toward a severe or critical phase. A good knowledge of the potential risk factors is essential for clinicians to distinguish high risk patients and a prioritized approach to prevent disease progression and unfavorable consequences [4]. Male, older people, and individuals of any age who show serious underlying comorbidities such as cardiovascular diseases, diabetes, pulmonary diseases, tumors, and immunodeficiencies are at increased risk for progression of severe disease as a result of SARS-CoV-2 infection [4, 5]. Meanwhile, poor oral health status can raise the risk of advanced serious medical conditions. Consequently, it has been reported that promoting oral health in patients of any age, by lowering their risk of advanced non-oral

systemic diseases, may decrease the morbidity due to COVID-19 infection [5].

First of all, recent studies have shown that since salivary glands, the epithelial lining of salivary ducts, and oral mucosa have higher levels of angiotensin-converting enzyme-II (ACEII) expression, they are initial target cells for coronavirus, and therefore SARS-CoV-2 can colonize in the mouth [6, 7]. Moreover, the oral cavity is the common entry and exit point for many viral infectious diseases through droplets and aerosol and it harbors various pathogens [8]. As a result, it has a conducive ecosystem for colonization of potential respiratory pathogens in the periodontium, gingival crevicular fluid (GCF), salivary glands (major or minor), and lower and upper respiratory tract [6, 7, 9]. The last evidence is related to the ciliary actions in the airways lining that spillover microorganism from the mouth to the respiratory tissues and vise-versa [6, 7]. Consequently, oral hygiene is important as the same scale as hand hygiene in COVID-19 pandemic management, and governments, authorities, and the media should emphasize oral hygiene guidelines [6].

This study aimed to perform a systematic literature review to develop a better understanding of the influence of the oral health status on the COVID-19 severity by analyzing data and information from existing scientific studies. This study was intended to address the question, "How does poor oral health status impact the severity of COVID-19 patients?" which may highlight the importance of oral health in the policy decisions, continued research, monitoring, surveillance, and other aspects of health.

METHODS

Data Source

In July 2021, a systematic literature review of published, peer-reviewed articles was conducted to investigate the independent variable oral health status in comparison to the severity of the dependent variable, COVID-19.

Vital statistics were retrieved from the Centers for Disease Control and Prevention website (https://www.cdc.gov), and the World Health Organization website (https://www.who.int). A systematic search of the medical literature of online databases including PubMed/Medline, Ovid Medline,

SCOPUS, Cochrane database, and Google Scholar was done from the 1st of December, 2019 to 30th of July, 2021. The medical subjects heading (MeSH) used terms were: COVID-19 OR coronavirus OR novel coronavirus OR SARS-CoV-2 OR SARS CoV 2 in combination with terms "severe COVID-19", "oral health", "oral disease", "oral hygiene", "oral bacteriom", "periodontitis", "periodontal disease", "caries", "dental public health" and the Boolean operators "AND" and "OR" to perform database searches. A staged literature search was conducted, while a separate literature search was carried out for each section within this study, and all the relevant articles were identified and summarized individually in a table.

Ethical Considerations

Since this study is a systematic literature review, it did not require institutional review board (IRB) approval.

Inclusion Criteria

Studies were included if they focused on the oral health status and COVID-19 relationship. To attain the highest level of credibility, only peer-reviewed, scholarly research articles were chosen for analysis and inclusion in this paper. Additionally, only articles written in the English language were selected and used. No limit has been placed on the participants in this study (e.g., age, gender, race, or ethnicity).

Exclusion Criteria

Exclusion criteria were articles with no particular description of the role of oral health in the severity of COVID-19 infection.

Data Collection Procedures

During the preliminary step of collecting relevant studies, titles and/or subjects mentioning variations of the search terms were obtained for further assessment (n = 352). After reading the abstracts, results, and discussion sections, articles were collected for comprehensive reading (n = 150). Some articles were excluded (n = 125) since they did not fulfill the inclusion criteria. A comprehensive review of the articles leads to the selection of 25 articles for inclusion in this paper. Figure 1 presents a detailed description of the process of selecting the articles for this project (Figure 1).
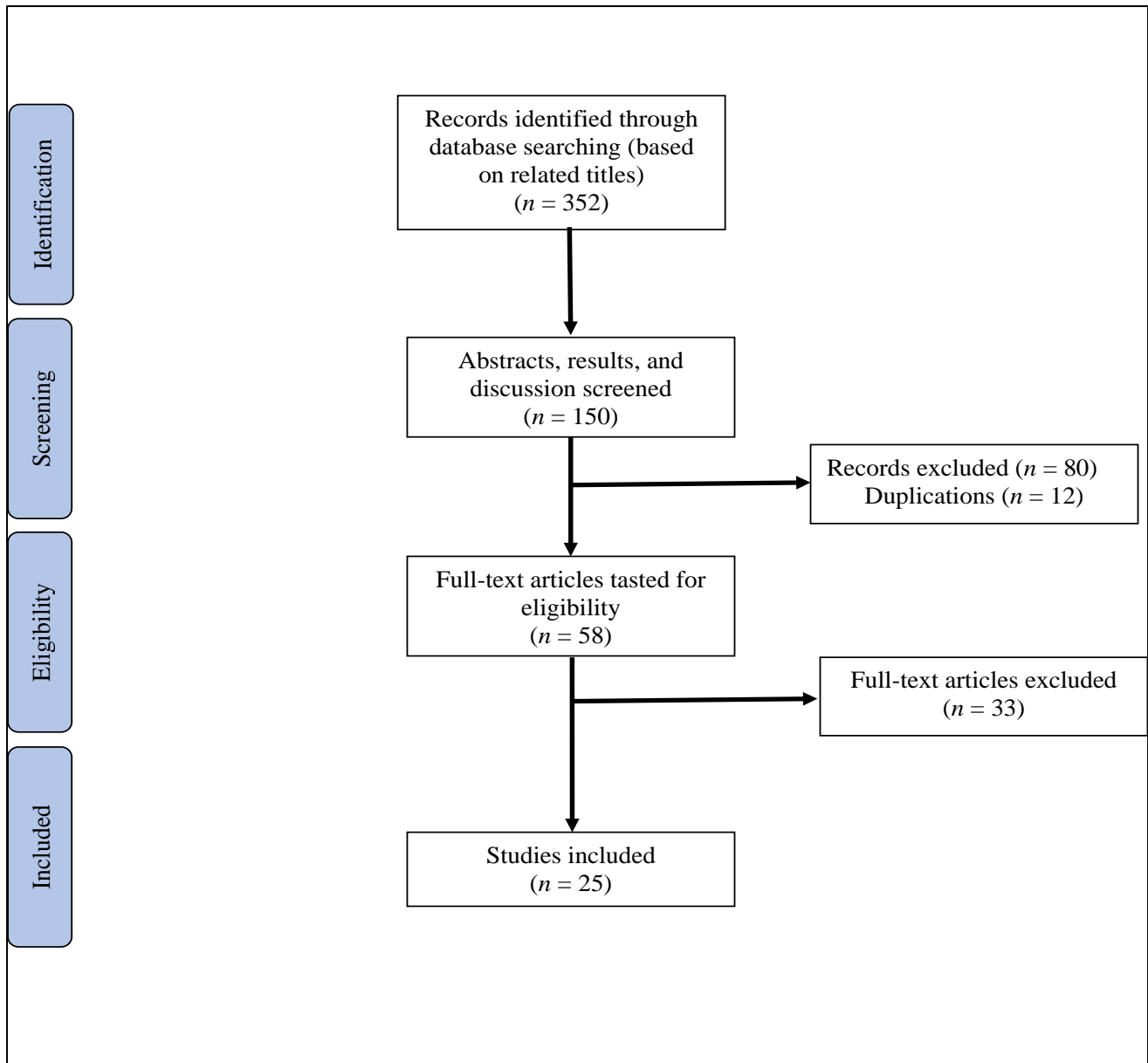
Figure 1: Flow diagram of literature search and selection steps (adapted from PRISMA)

For each of the 25 selected articles, summaries including descriptive details (authors and year published) and main findings were extracted and placed into an organized data table (Table 1).

DATA ANALYSIS AND RESULTS

Table 1: Article Summaries

Author, Year		Summary and Results
Aquino-Martinez, Hernándz-Vigueras, 2021 [10]		• Gram-negative periodontal bacteria worsen senescent cell cumulation in the lungs and progress SARS-CoV-2 replication. • Antiviral mouth rinses decreased the oral viral load and prevent COVID-19 dissemination. • Identification of active severe periodontitis can be a reliable indicator for risk classification in elderly COVID-19 patients.
Bains, V. K., & Bains, R., 2020 [6]		• Oral hygiene and hand hygiene have similar importance during the COVID-19 pandemic. • Higher expression of ACEII receptors is observed in salivary glands, the epithelial lining of salivary ducts, and oral mucosa which are known as primary targets for coronavirus, and consequently, SARS-CoV-2 can colonize in the oral cavity. • Probable transmission of SARS-CoV-2 will be reduced in case of careful oral hygiene in patients suffering from severe COVID-19.
Balaji, *et al.,* 2020 [11]		• Higher levels of protease (furin and cathepsin) in chronic periodontitis and oral cancer are associated with a greater affinity of SARS-CoV-2 to ACEII receptors resulting in an increased risk of COVID-19 infection. • Melatonin reduces the inflammation with disturbance of the cathepsin-mediated fusion of virus and host cell. • Patients with chronic periodontitis and oral cancer have lower amounts of melatonin.
Bao, *et al.,* 2020 [12]		• There is a close association between the oral opportunistic pathogens and SARS-CoV-2 co-infections in the lungs. • More co-infections risk factors including poor oral hygiene, cough, excess inhalation, and mechanical ventilation can be observed among COVID-19 patients. • Higher proliferation of anaerobes and facultative anaerobes with the main source of oral microbiota is associated with lung hypoxia, which is reported as the common symptom in COVID-19 patients.
Botros, *et al.,* 2020 [5]		• Inflammatory cytokines and microbial products against oral infection influence on inflammation of long distant organs. • Lung infection will be worsened when oral pathogens are aspirated into the lower respiratory system. • The oropharyngeal accumulation of virus and the probable risk of severe COVID-19 might be reduced by careful oral hygiene.
Campisi, *et al.,* 2021 [13]		• The correlation between chronic periodontitis and COVID-19 might be explained in two ways: directly; virus use the ACEII and CD147 receptors to infect the host cells; and indirectly; the higher expression of inflammatory biomarkers, especially IL-6 and IL-17.
Casillas Santana, *et al.,* 2021 [14]		• Cytokine storm leading to inflammation in periodontal infections in patients suffering from COVID-19 might be a result of adverse effects of SARS-COV-2 including ARDS or failure of multiple organs.• Periodontal disease can elevate blood sugar levels, causing the body to operate at hyperglycemic levels for prolonged periods of time, disturbing the function of immune system and increasing virus replication. • The ACEII receptors expression is increased in diabetes associated with periodontitis. • Overexpression of ACEII receptors is related to mild-to-severe COVID-19.

Author, Year	Summary and Results
Fabri, 2020 [15]	• Periodontitis as a chronic disease leads to cytokine hyper-reactivity, with an effect on systemic inflammatory-immune responses. Also, can result in T-cells dysregulation. • Periodontal dysbiosis can generate bacterial co-infection in the respiratory tract. • Tissue damage and pulmonary inflammation as a result of persistent production of cytokines and chemokines, bacterial co-infection, and immune dysfunction could be the main reasons for severe COVID-19 in patients with periodontitis.
Herrera, et al., 2020 [39]	• There are three explanations for impact of the oral viral load of SARS-CoV-2 on the COVID-19 severity: (1) At the first ten days, accumulation of SARS-CoV-2 usually is reported in the nasal, oral, and pharyngeal tissues; (2) A higher number of ACEII receptors is reported in the salivary glands rather than the lungs; (3) salivary droplets are the most relevant way for the COVID-19 transmission. • Decreased oral viral load may be related to the lower degrees in the severity of the COVID-19 disease.
Kamel, et al., 2021 [16]	• Subgroup assessment of severe COVID-19 patients according to deterioration timing showed that individuals with first and second-week deterioration had significant poor oral hygiene. • Patients with poor oral health had a significant delayed recovery period when compared to other cases. • Levels of C-reactive protein was significantly high in patients with poor oral health reflecting a severe COVID-19.
Kara, et al., 2020 [17]	• Galectin-3 spike proteins are essential to enter the SARS-CoV-2 into host cells. • Higher level of Galectin-3 is associated with severe periodontitis. • Periodontitis and severe COVID-19 infection may have a close association due to Gal-3-mediated enhanced immunological response, viral attachment, and the development of other systemic diseases as a result of periodontitis.
Larvin, et al., 2020 [18]	• There was not a significant risk of COVID-19 in patients with painful or bleeding gums and loose teeth in comparison with control groups. • A higher risk of mortality was reported in COVID-19 patients with painful or bleeding gums but not loose teeth cases. • Patients with periodontal problems showed a higher risk of mortality following COVID-19. • Although Periodontal disease may not lead to a higher risk of COVID-19 directly, it may be associated with COVID-19 pathology and raise the risk of mortality.
Lloyd-Jones, et al., 2021 [19]	• Saliva as a reservoir of SARS-CoV-2 is able to enter the vasculature system including the lung periphery through the gingival sulcus or periodontal pocket, then binds to the ACEII receptor and leads to lung parenchymal damage. • Accumulation of dental plaque and periodontal inflammation may aggravate the above pathway. • Reducing the salivary viral loads by simple low-cost interventions such as daily oral hygiene should be prioritized to prevent severe COVID-19.

Summary and Results	Author, Year
• ACEII expression increases in periodontal disease. Giving rise to this receptor is responsible for several acute inflammatory injuries. • The entry of SARS-CoV-2 into the mouth may be simplified following higher expression of ACEII protein in cases of periodontal disease which can progress the disease to severe COVID-19.	Mancini, *et al.*, 2020[20]
• Patients with periodontitis showed COVID-19 complications such as mortality, intensive care unit (ICU) hospitalization, and mechanical ventilation. • There was a significant link between biomarker levels to severe COVID-19 outcomes such as white blood cell, D-dimer, and C Reactive Protein (CRP) in COVID-19 cases associated with periodontitis.	Marouf, *et al.*, 2021 [21]
• There is an association between periodontitis and many chronic diseases which all of them have been described as probable risk factors of severe COVID-19 including hypertension. • Periodontal tissues are extensive entry point for many pathogens including SARS-CoV-2. • A greater level of ACEII receptors on the oral mucosa have been reported in cases of COVID-19 infection associated with periodontitis.	Martu, *et al.*, 2020 [22]
• Even in the absence of COVID-19, the risk of pneumonia in patients with diabetes and periodontitis is significant. • Oral hygiene considerably in diabetic patients could minimize the possible systemic consequences of COVID-19 infection.	Pfützner, *et al.*, 2020 [23]
• It has been reported that elderly patients are at the highest risk for periodontal disease and also, are for severe COVID-19. • Diabetes is a significant common predictor for severe COVID-19 and periodontal diseases due to higher expression of ACEII receptors. • Additionally, periodontal disease predisposes individuals to hypertension and cardiovascular disease which are among the main comorbidities in COVID-19 infection.	Pitones-Rubio, 18. *et al.*, 2020 [24]
• Oral cavity mucosa might be a presents a potential route of SARS-CoV-2 due to its high expression of ACEII receptors. • Povidone-iodine and cetylpyridinium chloride-based oral rinses exhibit virucidal action and may be used to prevent COVID-19 infection. • A greater risk of complications from SARS-CoV-2 is reported in patients with periodontitis. • Periodontitis is observed with pneumonia in hospitalized COVID-19 patients due to bacterial infections aspirating from the mouth.	Sanz, 2021 [25]

Author, Year	Summary and Results
Sampson, *et al.,* 2020 [26]	• Greater amounts of oral bacteria rise the probable oral pathogens aspiration into the lungs. • Periodontal disease-related enzymes alter the surfaces of oral mucosal; prepare them for accumulation of respiratory pathogens. • Respiratory epithelium may be changed by periodontal-related cytokines to encourage infection by respiratory pathogens. • COVID-19 infection results in imbalances in the oral microbiome and higher risk of periodontal disease.
Shamsoddin, 2021 [27]	• COVID-19 complications were experienced by 12.8 % of individuals with periodontitis and 2.2 % those without periodontitis. • COVID-19 patients with periodontitis showed a greater level of inflammatory blood marker compared to cases without periodontitis. • The virulence of the SARS-CoV-2 may increase if the expression of cellular receptor elevates. • Periodontal pockets act as viral reservoirs.
Sirin, & Ozcelik, 2021[28]	• In patients with a higher dental damage stage, a greater morbidity/mortality due to COVID-19 is reported. • The probable link between weakness of immune system and morbidity/mortality due to COVID-19 may imply an indirect connection between the dental damage stage and the function of immune system.
Sukumar, & Tadepalli, 2021 [29]	• Inter-bacterial exchange between the lungs and the oral cavity leads to a higher risk of bacterial super infection in COVID-19 patients. • Periodontitis and poor oral hygiene impair the symbiotic interactions of oral microorganisms and elevate the production of pro-inflammatory cytokines. • Cytokine storm is linked to severe COVID-19 outcomes. • Expression of ACEII receptors in different oral epithelial cells showed that the mouth is an important reservoir for SARS-CoV-2. • Careful oral hygiene in hospitalized patients may inhibit the accumulation of dental plaque, decrease bacterial loads, prevent aspiration of oral pathogens, and lower the risk of pneumonia.
Takahashi, *et al.,* 2021 [9]	• Periodontitis is associated with respiratory, diabetes, and cardiovascular disease. An increased COVID-19 aggravation rate and mortality is reported in patients with these diseases. • Poor oral hygiene produces COVID-19 aggravation by provoking the ACEII receptors expression and higher inflammatory cytokines in the lower respiratory tract. • Long-term hospitalization of patients with severe COVID-19 deprives them of careful oral care which may increase the aggravation risk of infection in the lower respiratory tract.
Zhong, *et al.,* 2020 [30]	• ACEII and furin receptors enhance the SARS-CoV-2 fusion with host cell membranes. • Higher expression of furin and ACEII receptors in epithelial cells of the mouth implies the probable transmission of COVID-19 through the oral mucosa.

DISCUSSION

This systematic literature review presents evidence that poor oral health status is correlated to severe COVID-19 complications. Individuals with a higher dental damage stage had higher morbidity/mortality due to COVID-19 [28]. First and second-week deterioration and delayed recovery periods were significantly more in individuals with poor oral health than those with good health [16]. Additionally, COVID-19 people with periodontitis were at significant risk of ICU hospitalization, need for mechanical ventilation, and mortality compared to patients without periodontitis [21].

Among oral diseases, dental caries and periodontal disease are greatly prevalent all over the world [31]. However, the literature review findings reveal that most studies examined the relationship between periodontal problems and COVID-19 infection. The first reason could be related to the various systemic effects of periodontitis. Studies found that periodontal disease predisposes individuals to hypertension, cardiovascular disease, diabetes, pneumonia, and COPD [32, 33] which are between the major risk factors for severe COVID-19 infection [34, 35]. Studies also showed that chronic inflammation, metastatic infection, and vascular injury endotoxins are all potential oral cavity–based etiologies of cardiovascular diseases [36]. It is well proven that the association between diabetes and periodontitis is bidirectional [24, 33, 36]. Periodontal disease also causes the body to operates at hyperglycemic levels for prolonged periods of time which impairs the function of the innate immune system and raises virus reproduction [14].

According to the literature review findings, the oral cavity, especially saliva, dental plaque, and periodontal pocket in patients with periodontal disease, are considered as suitable reservoirs for the various pathogens to accumulate, proliferate, and spread to the lower airways [27, 33, 37]. Studies reported that periodontal dysbiosis and aspiration of mouth pathogens into the lower respiratory tract can exacerbate lung infection in COVID-19 patients through bacterial co-infection [5, 10, 12, 15, 26].

The literature review findings also reveal that oral inflammation, as is common in periodontal disease, can result in systemic inflammation [33]. Overexpression of inflammatory cytokines or cytokine storm is associated with adverse outcomes in COVID-19 patients such as acute respiratory disease (ARD) and multiple organ failure [9, 14].

As shown in the literature review, the increased expression of ACEII receptors is associated with mild-to-severe COVID-19 infection [14, 38]. Salivary glands, the epithelial lining of salivary ducts, and oral mucosa have higher levels of ACEII expression; as a result, they are initial target cells for the coronavirus and the oral cavity is a proper conducive ecosystem for its colonization [6, 39]. Moreover, ACEII overexpression was reported in periodontal disease and diabetes associated with periodontitis [9, 13, 14, 20, 22, 24, 25, 30]. Increased levels of furin and cathepsin also in chronic periodontitis and oral cancer can facilitate the affinity of SARS-CoV-2 to ACEII receptors [11].

The literature review highlights the importance of implementing preventative and therapeutic strategies to minimize the worldwide burden of oral disease [25]. Knowing that periodontal disease is related to severe COVID-19 might assist to recognize the high risk groups and develop appropriate recommendations [24]. A simple strategy to combat the coronavirus crisis may be monitoring and maintaining the oral health [23]. Simple low-cost interventions such as daily oral hygiene should be prioritized since they can reduce the salivary viral loads [19]. Additionally, it is important to keep periodontitis under control and maintain meticulous oral hygiene to decrease virus oropharyngeal colonization [5, 17]. Accurate oral hygiene also is necessary for quarantine and isolation facilities, and also in hospitalized COVID-19 patients to prevent COVID-19 dissemination [6, 10].

CONCLUSION

This systematic literature review presents evidence that poor oral health status is associated with severe COVID-19 complications. COVID-19 patients with poor oral health status were at a higher risk of ICU hospitalization, need for mechanical ventilation, first and second-week deterioration, delayed recovery period, and mortality. Predisposing individuals to serious systemic diseases, conducting pathogens to the lower airways, developing bacterial co-infection, impairing the function of the innate immune system, increasing expression of ACEII receptors, and enhancing expression of inflammatory cytokines are oral-related risk factors for severe COVID-19 infection.

Oral hygiene is important as the same scale as hand hygiene in COVID-19 pandemic management, and governments, authorities, and the media should emphasize oral hygiene guidelines. Monitoring and maintaining oral health, identifying risk groups, and developing appropriate recommendations are simple strategies to combat the current coronavirus crisis.

Conflict of Interest: Nil.

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