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Original Article

Oral Health and the Risk of COVID-19: A Systematic Review and Meta-analysis

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Abstract : The importance of oral health care in respiratory infections has been highlighted in the past. Several recent studies have revealed the association between COVID-19 and oral health. This paper aims to comprehensively analyse the risk of COVID-19 with respect to oral health. The search was performed on 12 July 2021 using Embase and Medline. Cohort, case-control, and cross-sectional studies were included in this study. The Newcastle-Ottawa scale was used to qualitatively assess the risk of bias. The data were used for the odds ratio calculation, followed by the unadjusted value and 95% confidence interval. Five studies (one cohort, one case-control, and three cross-sectional studies) considered in this review included 16,721 participants. In the group with poor oral health, the incidence was 1.97 (0.93~4.16), the severity was 14.01 (4.89~40.20), the hospitalization rate was 2.01 (1.2~3.07), and the mortality was 1.41 (0.64~3.11) times higher than in the group with good oral health. Poor oral health increases the risk of COVID-19. To reduce the risk of COVID-19, comprehensive oral management guidelines are urgently required. Policymakers should establish appropriate countermeasures according to the national situation.

Keywords : COVID-19, Oral health, Meta-analysis, Observational study

INTRODUCTION

In December 2019, a case of an unknown type of pneumonia was detected in Wuhan, Hubei Province, China. The causative virus was extracted from human patients and was found to be a novel coronavirus through molecular analysis [1]. The virus was named “severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)” by the International Committee on Taxonomy of Viruses [2]. Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 is the most urgent and pressing health issue worldwide [3]. The

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most common clinical features include cough, fever, headaches, sore throat, and myalgia, similar to those caused by common respiratory viruses [4]. Some patients might experience severe clinical symptoms, such as severe pneumonia and multi-organ failure, that require critical care [5]. According to Wu (2020), the probability of developing severe symptoms was 5%, and the case fatality rate was reportedly 2.3% [6]. In particular, complications and mortality from COVID-19 further increased in vulnerable groups with hypertension, diabetes, chronic obstructive pulmonary disease, and cerebrovascular disease [7].

The importance of oral health care in respiratory infections has been highlighted in the past. Scannapeico (2003) reported that poor oral hygiene and periodontal disease were positively associated with nosocomial pneumonia [8]. Azarpahooh (2006) reported that frequent oral health care reduced the incidence and progression of respiratory diseases among high-risk elderly groups living in nursing homes and those in intensive care units [9]. Gomes-Filho et al. (2020) reported that periodontitis and respiratory diseases (e.g., pneumonia, COPD, and asthma) showed a positive association [10]. With the outbreak of COVID-19, the importance of oral health care, which is closely related to the respiratory system, is being highlighted. Among COVID-19 patients, those with poor oral health reportedly had more severe symptoms and a longer recovery period [11]. Reportedly, periodontitis was positively associated with ICU admission, assisted ventilation, and mortality due to COVID-19 [12,13]. Additionally, it is hypothesised that poor oral condition in patients with COVID-19 increases the risk of bacterial superinfection [14]. Therefore, the importance of oral care needs to be further emphasized at this point.

Recently, associations and hypothetical mechanisms between oral health and COVID-19 have been proposed [3,15]. However, to the best of our knowledge, there is currently no systematic review and meta-analysis that comprehensively analyses the risk of COVID-19 with respect to oral health. The aim of this study was to analyse the risk of COVID-19 based on differences in oral condition.

METHODS

1. Protocol registration and search strategy

This systematic review was conducted in accordance with PRISMA statements [16]. PRISMA 2020 guidelines provide 27 checklists and 4-step flow charts of evidence-based minimum item sets for reporting in systematic review and meta-analysis [16]. The protocol for this study was registered with PROSPERO. The search was performed on 12 July 2021 using Embase and Medline. The search was performed by adding related search terms based on the mesh term. The authors discussed amongst themselves to finalise the search words. The search terms were as follows: (periodontal:ab,ti OR periodontitis:ab,ti OR gingiva:ab,ti OR gingivitis:ab,ti OR 'gingiva disease':ab,ti OR oral:ab,ti OR mouth:ab,ti OR tongue:ab,ti corona:ab,ti OR 'coronavirus disease 2019':ab,ti OR covid:ab,ti OR 'coronavirus':ab,ti OR 'covid 19':ab,ti 'disease severity':ab,ti OR severity:ab,ti OR symptom:ab,ti OR pain:ab,ti OR outcome:ab,ti OR prognosis:ab,ti OR 'hazard ratio':ab,ti OR 'odds ratio':ab,ti OR survival:ab,ti OR mortality:ab,ti OR fatality:ab,ti OR death:ab,ti) AND ([humans]/lim AND [english]/lim AND ([article]/lim OR [article in press]/lim OR [review]/lim).

2. Study selection and data extraction

We included studies that presented the number of samples or effect measures (e.g., odds ratio, and hazard ratio) related to COVID-19 according to oral health. Cohort, case-control, and cross-sectional studies were eligible for inclusion in this study. Only human studies were included, and conference papers and review papers were excluded from analysis. We did not have restrictions by language or year of publication. Two authors (JJ and JP) conducted the literature search and checked the title and abstract of each study independently. The same authors reviewed full-text articles for inclusion. Any disagreements were resolved through discussion. We extracted the following data in the screening phase: title, abstract, journal, author name, publication year, and publication type. Additional information on study design, WHO region, number of samples, effect measures, and age were extracted through a full-text assessment.

3. Assessment of risk of bias

The Newcastle-Ottawa scale was used to qualitatively assess the risk of bias for the included cohort and case-control studies [17]. For cross-sectional studies, the adapted version of the Newcastle-Ottawa scale presented by Herzog et al. was used [18]. The Newcastle-Ottawa scale is one of

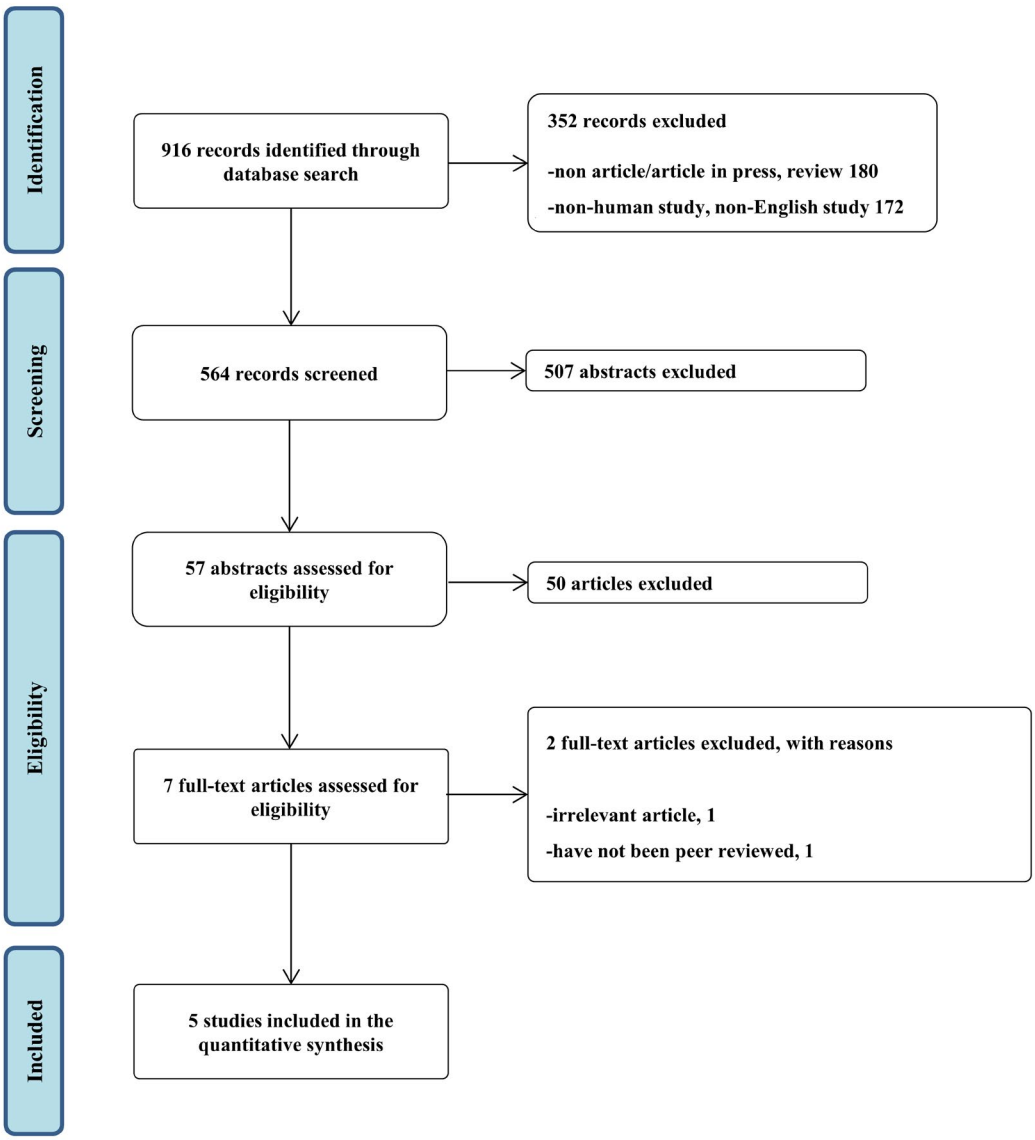

Fig. 1. PRISMA flowchart.

the most widely used tools for assessing the bias risk of observational studies [19]. It is a widely validated tool that allows researchers to rapidly evaluate research across a variety of disciplines and facilitates meta-regression analyses [19]. The authors (JJ and JP) independently assessed the risk of bias of the studies included. Any disagreements were resolved through discussion. Cohort and case-control study scores were graded as 'good', 'fair', and 'poor' according to the Agency for Healthcare Research and Quality (AHRQ) standard. We evaluated the study quality by establishing a criterion similar to the AHRQ standard for cross-sectional studies.

4. Data synthesis and subgroup analysis

Since adjusted variables are different for each paper included in the analysis, meta-analysis using the adjusted variables may limit the interpretation of results [20]. We tried to derive statistical results using unadjusted variables. The data were used first for the odds ratio calculation, followed by the unadjusted value and 95% confidence interval. The classification of I^2 statistics, as presented by Higgins et al., was used to evaluate the heterogeneity of the effect measures [21]. Heterogeneity was considered low, moderate, and high for I^2 values of 25%, 50%, and

75%, respectively. If the heterogeneity exceeded 50%, the random effect method was used; otherwise, the fixed-effect method was used. If an integrated value was required within the study, calculations were performed using the Higgins method [21]. Forest plots were drawn to clearly visualise the synthesised risk. Review Manager 5.4 software developed by Cochrane Training in London, U.K. was used to synthesise the results. We analysed the risk of COVID-19 according to oral health in four categories: incidence, severity, hospitalisation, and mortality.

RESULTS

1. Study Selection

We identified 916 papers through database search and screened 564 papers; 507 were excluded on the basis of the title and abstract, and 57 were selected for detailed assessment. After evaluating the details, 50 were excluded because their results did not present an association between COVID-19 and oral health, or their study designs were not pertinent. Of the seven full-text articles, five were finalised for this study, excluding articles that were irrelevant or not peer-reviewed (Fig. 1).

2. General characteristics of included studies

The five studies considered in this review included 16,721 participants. Of the five studies identified, one was case-control, one was a cohort, and three were cross-sectional. The characteristics of the included studies are summarised in Table 1.

3. Association between COVID-19 and oral health

Four results were included in the analysis for COVID-19 incidence. The incidence of COVID-19 was 1.97 (0.93 ~4.16, $p=0.08$, $I^2=96\%$) times higher in the group with good oral health compared to the group with poor oral health, but this was not statistically significant (Fig. 2). Three results were included in the analysis for COVID-19 severity. The severity of COVID-19 was 14.01 (4.89~40.20, $p<0.001$, $I^2=67\%$) times higher in the group with good oral health than in the group with poor oral health (Fig. 3). Five results were included in the analysis for COVID-19 hospitalization rate. The hospitalization rate of COVID-19 was 2.01 (1.02~3.07, $p=0.04$, $I^2=89\%$) times

Table 1. Characteristic of included studies

Author, year	Study design	WHO region	Number of samples	Oral health assessment	Type of effect measures
Kamel, 2021 [11]	Cross-sectional	Egypt	308 COVID-19 patients	Oral health Good / Fair / Poor	Severity
Marouf, 2021 [12]	Case-control	Qatar	Cases 40 (with COVID-19 complications) Controls 528 (without COVID-19 complications)	Periodontitis Stage 0-1: healthy Stage 2-4: Periodontitis	Severity (Assisted ventilation) Hospitalization (ICU admission) Mortality
Sirin, 2021 [42]	Cross-sectional	Singapore	137 COVID-19 patients	Dental damage Stage 0, 1, 2, 3	Severity (Symptom) Hospitalization
Katz, 2021 [43]	Cross-sectional	U.S.A.	1468 recurrent aphthaous stomatitis patients 987 hospital controls	Recurrent aphthaous stomatitis ((+ / −)	Incidence
Larvin, 2020 [13]	Cohort	U.K.	Total n = 13,254 1,616 COVID-19 positive 11,637 COVID-19 negative	Painful gums (+ / −) Bleeding gums (+ / −) Loose teeth (+ / −)	Incidence (COVID-19 test) Hospitalization Mortality

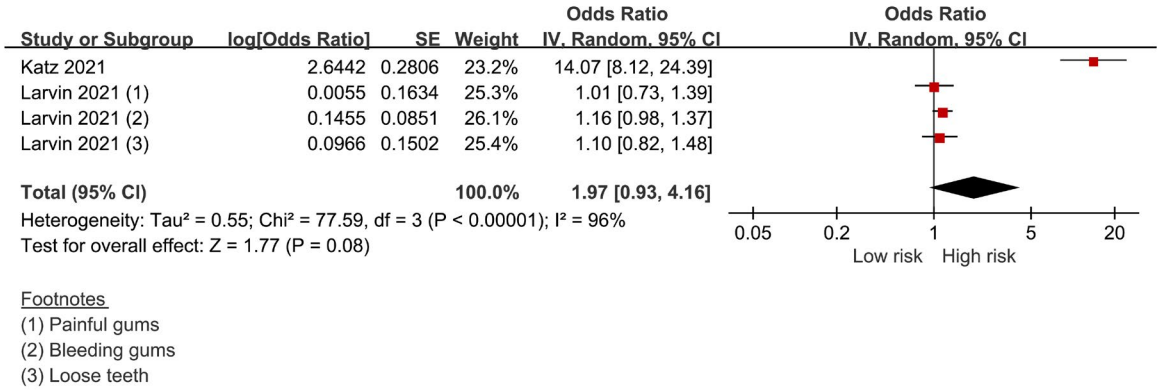

Fig. 2. The forest plot for incidence of COVID-19 according to oral health.

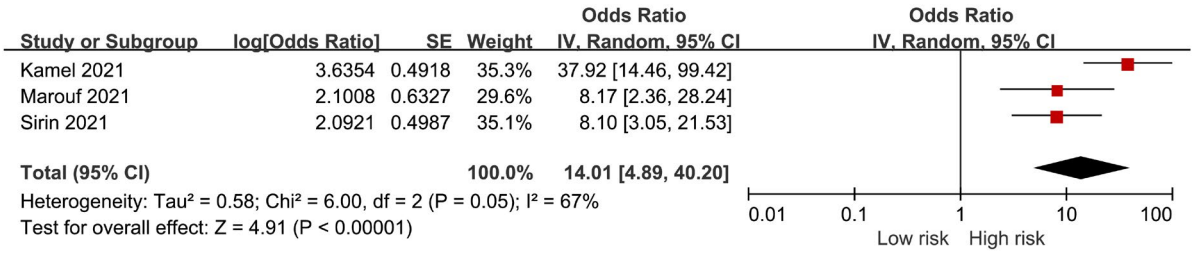

Fig. 3. The forest plot for severity of COVID-19 according to oral health.

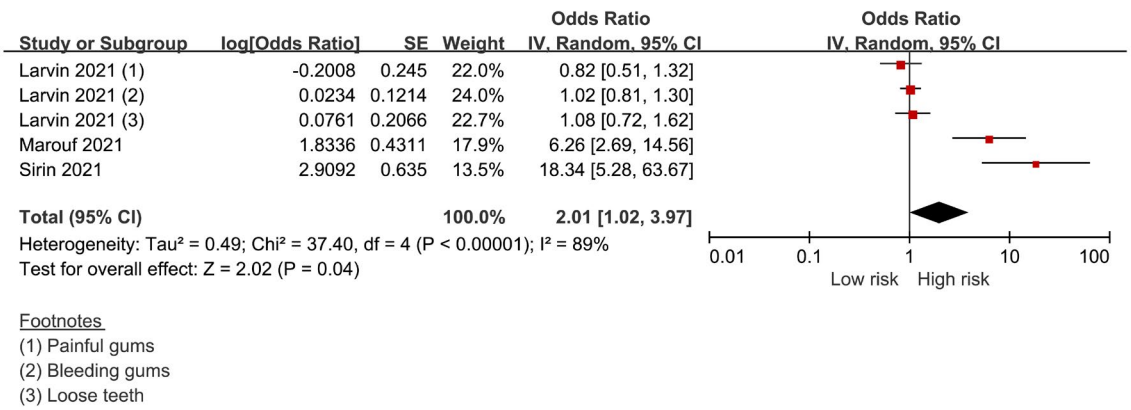

Fig. 4. The forest plot for hospitalization of COVID-19 according to oral health.

higher in the group with good oral health than in the group with poor oral health (Fig. 4). Four results were included in the analysis for COVID-19 mortality. The mortality rate of COVID-19 was 1.41 (0.64~3.11, $p=0.40$, $I^2=80\%$) times higher in the group with good oral health than in the group with poor oral health (Fig. 5).

4. Risk of bias within studies

Three out of the five studies included were rated as 'good' and two as 'poor'. Detailed assessments are presented in Table 2.

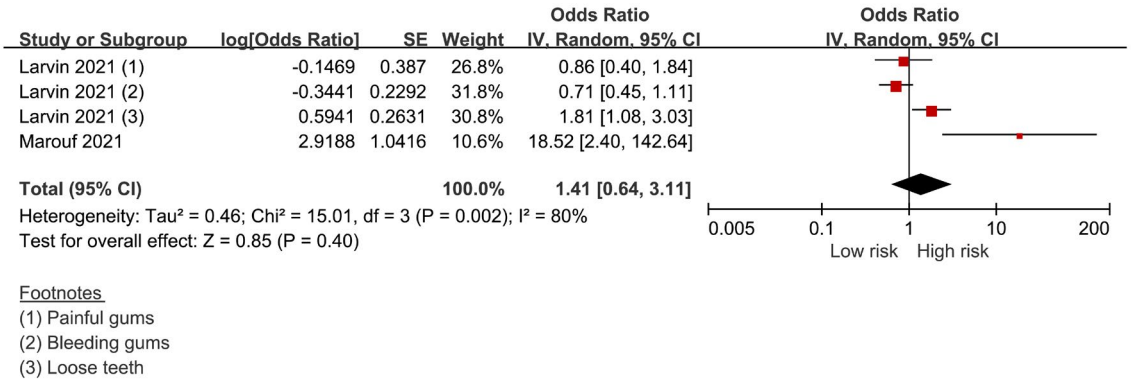

Fig. 5. The forest plot for mortality of COVID-19 according to oral health.

DISCUSSION

In this systematic review and meta-analysis, we categorised the risk of COVID-19 into four sub-groups and analysed their association with oral health. The main finding of this study was that poor oral health was positively associated with the overall risk of COVID-19. In particular, the severity of COVID-19 displayed a shocking result that increased by approximately 14 times. This study is the first comprehensive analysis of oral health and the risk of COVID-19.

Lower respiratory infections are caused by ingestion of oral secretions, including microorganisms, or contamination of the lower airway epithelium by microorganisms contained in aerosolized droplets [22]. Several mechanisms suggest connection between oral health and respiratory infections; 1) cytokines and enzymes produced by a periodontal disease may change the epithelium of the respiratory tract into an environment susceptible to infection, 2) Periodontal disease-related enzymes may destroy the saliva pellicles on bacteria preventing removal from mucosal surfaces. and 3) Direct inhalation of oral pathogens into the lungs [3,14]. Periodontitis and tooth decay are the most common oral diseases [14]. Transfers to these conditions may lead to the breakdown of the balance of oral bacteria (primarily *Streptococcus mutans*, *Prevotella intermedia*, *Fusobacterium nucleatum*, and *Porphyromonas gingivalis*), making it vulnerable to respiratory infections [3,14,22,23]. Therefore, inadequate oral hygiene may increase the risk of respiratory infections and potential post-viral bacterial complications.

Mechanisms similar to those underlying lower respiratory infections have been proposed in relation to oral health and COVID-19 infection, and several cytokines (e.g., interleukin, GM-CSF, IFN-gamma, TNF-alpha, and chemokines) specific to periodontitis and COVID-19 are being studied [3,24,25]. Several hypotheses on oral health and COVID-19 severity have also been suggested: Aspiration of periodontal bacteria may exacerbate COVID-19 by inducing the expression of angiotensin-converting enzyme 2 and inflammatory cytokines, receptors for SARS-CoV-2, in the lower respiratory tract [26]. Periodontal bacteria may cleave S glycoprotein to enhance SARS-CoV-2 virulence [26,27], periodontal pockets caused by periodontal disease can act as a viral reservoir [28]. Neutrophil extracellular trap production is implicated in the pathogenesis of both diseases [29] and Strong Th17 response in severe periodontitis may exacerbate the cytokine storm in COVID-19 [30]. These hypotheses provide feasibility for routine oral health care of COVID-19 patients across the medical field [31].

COVID-19 is now a global health problem that is rapidly spreading. Approximately 200 million people are infected with coronaviruses, and approximately 4.3 million people die from the infection (10 Aug 2021) [32]. Although efforts are being made to prevent infection and reduce hospitalization and mortality rate through vaccine development, it is difficult to fundamentally resolve the present situation due to the emergence of several variants of COVID-19 [33]. The primary mode of transmission is via aerosol, indirectly via fomites or droplets in the respiratory tract [34]. Currently, frequently washing hands, wearing a mask in public settings, and avoiding close contact are suggestively essential precautions for COVID-19 [35]. Oral hygiene, which can be the primary prevention gateway for most respiratory viral

Table 2. Risk of bias assessments for included studies – Newcastle-Ottawa Scale

Source (Cohort)	Selection				Comparability based on design and analysis	Outcome			Total	Assessment
	Representativeness of the sample	Selection of the non-intervention cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study		Assessment of outcome	Was follow up long enough for outcomes to occur	Adequacy of follow up of cohorts		
Larvin, 2020 [13]	1	1		1	2	1		1	7	Good

Source (Cross-sectional)	Selection				Comparability based on design and analysis	Outcome		Total	Assessment
	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of the exposure		Assessment of outcome	Statistical test		
Kamel, 2021 [11]	1	1	1	1		2	1	7	Poor
Sirin, 2021 [42]				1	2	2	1	6	Poor
Katz, 2021 [43]	1	1	1	1	2	2	1	9	Good

Source (Case-control)	Selection				Comparability based on design and analysis	Outcome			Total	Assessment
	Is the case definition adequate?	Representativeness of cases	Selection of Controls	Definition of Controls		Assessment of exposure	Same method of ascertainment for cases and controls	Non-response rate		
Marouf, 2021 [12]		1	1	1	2	1	1	1	8	Good

infections, is thought to be an essential action to reduce the risk of COVID-19 in the era of the COVID-19 pandemic.

We evaluated the risk of COVID-19 through four subgroups: incidence, severity, hospitalisation rate, and mortality. In particular, severity showed a striking result. Currently, due to the emergence of mutant viruses that are contagious or highly lethal, the severity of COVID-19 is more serious than in the early stage. Alpha-variants are highly transmissible and can increase hospitalisation and mortality rates [36,37]. The delta-variant is also highly contagious, potentially reducing the effectiveness of treatment [38-40]. In particular, the recently discovered lambda variant may reportedly have stronger resistance to neutralizing antibodies than other strains [41]. The increase in severity is prominent even when combined with the results of the current studies, which were primarily affected by the low-mutant, less-lethal coronavirus; the spread of the variants could further increase the severity over time. Therefore, a comprehensive oral care guideline is urgently needed to prepare for this situation, and a policy approach for each country is required.

Our study has a few limitations. First, all I^2 values were over 50%, indicating that the heterogeneity between the included studies was considerable. The potential causes are 1) different definitions and classifications of oral health, 2) different indications for severity and hospitalisation, and 3) selection bias may occur if results derived from the same registry are applied multiple times. Second, it is difficult to conclude the causal relationship between oral health and COVID-19 because the studies included were observational studies. Third, the effects of the confounding variables were not adjusted. Finally, the number of included studies and subjects was limited. Because the current COVID-19 pandemic period is short and the number of subjects is insufficient, long-term research through the establishment of a large-scale cohort is necessary.

CONCLUSION

Despite the limitations, this study highlights the importance of oral health in the primary prevention and severity reduction of COVID-19. In addition to basic preventive actions against COVID-19, such as regularly washing hands and wearing a mask, oral care is also supposedly essential. Comprehensive oral care guidelines are urgently required to reduce the risk of COVID-19. Additionally, policymakers should recognise the importance of oral care and establish appropriate countermeasures according to the national situation.

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