Evaluation of the Associations between Dry Mouth, Oral Lesions, and Orofacial Pain with COVID-19: A Systematic Review and Meta-analysis

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Abstract

Objectives: In patients with periodontal disease, the risk of COVID-19 is very high, so it is important to check oral health. Because the clinical manifestations of COVID-19 disease are not fully understood and the relationship between severity, mortality, and oral health is challenging, in the present study, we tried to investigate the relationship between clinical outcomes and COVID-19. Therefore, the present study evaluated the associations between the dry mouth, Oral lesions, and Orofacial pain with COVID-19.

Methods: The present study is based on PRISMA guidelines; all articles were published in international databases such as PubMed, Scopus, Science Direct, and Embase between March 2019 and May 2022. 95% confidence interval for effect size with random effect modal and REML were calculated. Meta-analysis of data collected from selected studies was performed using STATA.V16 software.

Results: In the initial review, the abstracts of 312 studies were reviewed, two authors reviewed the full text of 36 studies, and finally, 16 studies were selected. The prevalence of dry mouth and oral lesions in patients with COVID-19 was 39% (ES: 95% CI, 32 % to 46%) and 32% (ES: 95% CI, 22 % to 42%), respectively.

Conclusions: The prevalence of dry mouth in patients with COVID-19 was higher (39%) than oral lesions (32%) and orofacial pain (23%).

Keywords: COVID-19, Meta-analysis, Periodontal disease.

Introduction

On December 19, 2019, a new virus called SARS-CoV-2 was introduced, abbreviated to COVID-19, and spread very quickly and infected the whole world.[1] Worldwide, there have been 535,863,950 confirmed cases of COVID-19 as of 5:24 PM CEST on June 17, 2022, including 6,314,972 deaths, reported to the world health organization (WHO).

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As of June 16, 2022, 11,902,271,619 vaccine doses have been administered.[2] Common symptoms in people with COVID-19 include headache, mild shortness of breath, fever, and cough; Symptoms of diarrhea and vomiting, muscle aches, dry mouth, and sore throat may also occur in some patients. Evidence suggests that the oral cavity is associated with COVID-19 by salivary glands and ACE2 and TMPRSS2 receptors in oral mucosal epithelial cells.[1, 3] Studies have also shown that good oral hygiene can be linked to COVID-19 disease. According to a case report study, extensive gingival bleeding was observed in patients with COVID-19.[4] Study findings also showed that in patients rescued from COVID-19 disease, dry mouth and salivary gland ectasia are observed.[5] Therefore, according to the evidence in the existing literature, oral hygiene is very important to maintain a healthy condition. Periodontal disease (PD) can increase the inflammatory response in a person, and PD can increase the risk of systemic diseases.[6] COVID-19 disease has been reported to cause an inflammatory condition by releasing cytokines from host cells.[7] Previous studies have reported a direct relationship between periodontitis and respiratory diseases.[8] On the other hand, in the human oral cavity, more than 700 species of bacteria are observed in different parts, and it is mentioned as the second microbial community.[9] In patients with PD, the risk of COVID-19 disease is very high, so it is important to check oral health. Because the clinical manifestations of COVID-19 disease are not fully understood and the relationship between severity, mortality, and oral health is challenging, in the present study, we tried to investigate the relationship between clinical outcomes and COVID-19. Therefore, the present study evaluated the associations between the dry mouth, Oral lesions, and Orofacial pain with COVID-19.

Methods

Search strategy

The present study is a systematic review and meta-analysis based on PRISMA guidelines[10]. All publications published between March 2019 and May 2022 are included in international databases such as PubMed, Scopus, Science Direct, and Embase. Table 1 shows the PECO strategy and Google Scholar search engine used to find answers to the research questions.

The following search terms were used:

(((((((("Mouth"[Mesh] OR "Oral Mucosal Absorption"[Mesh] OR "Oral Medicine"[Mesh] OR "Pathology, Oral"[Mesh] OR ("Xerostomia/classification"[Mesh] OR "Xerostomia/complications"[Mesh] OR "Xerostomia/diagnosis"[Mesh] OR "Xerostomia/microbiology"[Mesh] OR "Xerostomia/pathology"[Mesh] OR "Xerostomia/statistics and numerical data"[Mesh] OR "Xerostomia/therapy"[Mesh])) AND "Lichen Planus, Oral"[Mesh]) AND "Facial Pain"[Mesh]) OR ("Facial Pain/classification"[Mesh] OR "Facial Pain/complications"[Mesh] OR "Facial Pain/diagnosis"[Mesh] OR "Facial Pain/microbiology"[Mesh] OR "Facial Pain/pathology"[Mesh] OR "Facial Pain/statistics and numerical data"[Mesh] OR "Facial Pain/therapy"[Mesh])) AND "Treatment Outcome"[Mesh]) AND ("COVID-19 "[Mesh] OR "SARS-CoV-2"[Mesh])) OR ("COVID-19 /microbiology"[Mesh] OR "COVID-19 /statistics and numerical data"[Mesh])) AND ("Periodontal Attachment Loss"[Mesh] OR "Periodontal Index"[Mesh] OR "Periodontal Diseases"[Mesh] OR "Periodontal Pocket"[Mesh] OR "Periodontal Cyst"[Mesh] OR "Periodontal Splints"[Mesh]).

Table 1. PECO strategy.

PECO strategy	Description
P	Population: COVID-19 patients
E	Exposures: COVID-19
C	Comparison: without COVID-19 or a control group
O	Outcome: Dry mouth, Oral lesions, Orofacial pain, and Periodontal diseases

Selection of Studies, Data Extraction, and Analysis Methods

Data were provided according to the first author's name, the number of participants, the mean age, and the methods used to evaluate oral health.

The Newcastle-Ottawa Scale (NOS) [11], which evaluates the quality of cohort and cross-sectional studies, case-control studies, and case series investigations, measures three dimensions (selection, comparability of cohorts, and outcome) with a total of nine items. Studies classified as low, medium, or high quality had NOS scores of 1-3, 4-6, and 7-9. STATA.V16 software was used to analyze the data. The level of heterogeneity was evaluated using the I2 index test (I2< 50% = low levels, 50<I2< 75% = moderate and I2>75% = high levels). The effect size's 95% confidence interval was calculated using the random effect modal and REML.

Results

Three hundred twelve studies were found when the current literature was reviewed using the study keywords. Duplicate studies were removed from the original review, and abstracts from 231 studies were reviewed. One hundred ninety-five papers were first removed because they did not match the inclusion criteria, and in the following stage, two authors reviewed the full texts of 36 studies. At this stage, 20 studies had been excluded from consideration for the study because of insufficient data, inconsistent study results, poor studies, a

lack of full-text access, and data that did not match the study's objectives. Finally, sixteen studies were selected (Figure1).

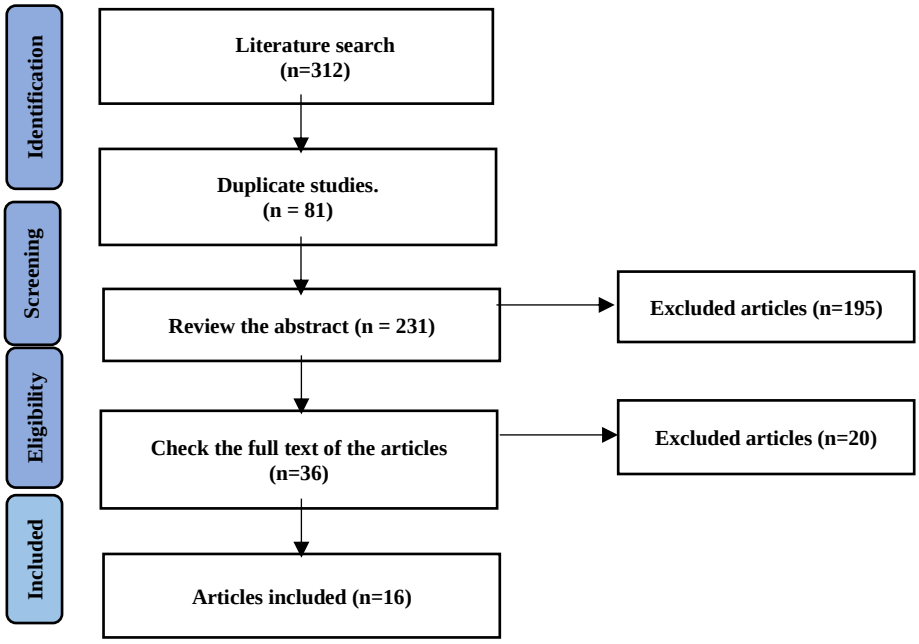

Figure 1. PRISMA flowcharts.

Characteristics

The present article includes eight cross-sectional studies and eight retrospective studies. 1005472 patients with a 53.08 average age (Table 2).

Bias assessment

According to the NOS instrument, the risk of bias was low and moderate in 7 and 9 studies, respectively (Table 3).

Table 2. A summary of the demographic data extracted from selected studies.

No.	Study. Years	Study design	Number of Patients	Mean of age (years)	Methods of assessing oral health
1	Katz et al., 2022 [12]	C.S	987849	68.2	Self-report
2	Villarroel-Dorrego et al., 2022 [13]	C.S	55	51	Clinical examination
3	Nuno-Gonzalez., 2021 [14]	C.S	666	56	Clinical examination
4	AbuBakr et al., 2021 [15]	C.S	573	36.1	Self-report
5	Favia et al., 2021 [16]	R	123	70	Clinical examination
6	Gherlone et al., 2021[5]	R	122	62.4	Clinical examination
7	Hocková et al., 2021[17]	R	9	64.3	Clinical examination
8	Kamel et al., 2021[18]	C.S	308	36.5	Self-report
9	Tandon et al., 2021[19]	C.S	419	37	Self-report

10	Marouf et al., 2021 [20]	C.S	568	42.9	Clinical examination
11	Biadsee et al., 2020 [21]	R	140	36.5	Self-report
12	Fantozzi et al., 2020 [22]	R	111	57.8	Self-report
13	Chen et al., 2020 [23]	C.S	108	52.1	Self-report
14	Freni et al., 2020 [24]	R	50	40	Self-report
15	Larvin et al., 2020 [25]	R	13502	68.5	Self-report
16	Sinjari et al., 2020 [26]	R	20	70	Self-report

Dry mouth

Prevalence of dry mouth in patients with COVID-19 was 39% (95% CI, 32 % to 46%) (I2=84.28%; P=0.00; high heterogeneity). These findings indicate that dry mouth is relatively common in patients with COVID-19. (Figure 2).

Oral lesions

Prevalence of oral lesions in patients with COVID-19 was 32% (95% CI, 22 % to 42%) (I2=94.99%; P=0.00; high heterogeneity). These findings indicate that oral lesions after dry mouth are relatively high in patients with COVID-19. (Figure 3).

Table 3. Bias assessment (NOS tool).

Study	Selection (5 scores)				Comparability (2 scores)	Outcome (2 scores)		Total scores
	Representative sample	Sample size	Non-respondents	Ascertainment of the exposure	Based on design and analysis	Assessment of outcome	Statistical test	
Katz et al., 2022 [12]	*	*	*	*	*	*	*	7
Villarroel-Dorrego et al., 2022 [13]	*	*	*	*	*	*	-	6
Nuno-Gonzalez., 2021 [14]	*	*	*	*	-	-	*	5
AbuBakr et al., 2021 [5]	*	*	*	*	*	-	*	6
Favia et al., 2021 [16]	*	*	*	*	*	*	*	7
Gherlone et al., 2021[5]	*	*	*	*	*	-	-	4
Hocková et al., 2021[17]	*	*	*	*	*	-	-	4
Kamel et al., 2021[18]	*	*	*	*	*	-	-	4
Tandon et al., 2021[19]	*	*	*	*	**	*	*	8
Marouf et al., 2021 [20]	*	*	*	**	**	*	*	9
Biadsee et al., 2020 [21]	*	*	-	*	*	-	-	4
Fantozzi et al., 2020 [22]	*	*	-	*	*	-	-	4
Chen et al., 2020 [23]	*	*	*	*	*	*	*	7
Freni et al., 2020 [24]	*	*	-	-	*	-	-	3
Larvin et al., 2020 [25]	*	*	*	*	*	*	*	7
Sinjari et al., 2020 [26]	*	*	*	*	*	*	*	7

*= 1 score; **= 2 score; -=0 score

Orofacial pain

Prevalence of Orofacial pain in patients with COVID-19 was 23% (95% CI, 12% to 34%) (I2=97.47%; P=0.00; high heterogeneity). These findings indicate that Orofacial pain is relatively low in patients with COVID-19. (Figure 4).

Periodontal diseases

Prevalence of Periodontal diseases in patients with COVID-19 was 5% (95% CI, 1% to 9%) (I2=1%; P=0.99; low heterogeneity). These findings indicate that oral lesions are relatively low in patients with COVID-19. Based on these findings, periodontal disease has a very low prevalence in COVID-19 patients, so it can be said that the association between the disease and periodontal disease is very small. (Figure 5).

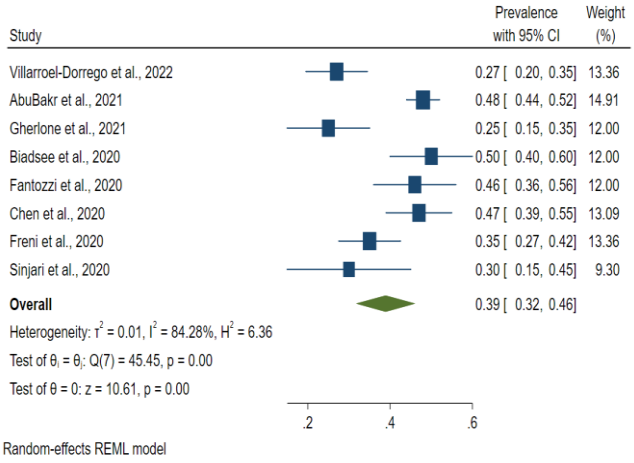

Figure 2. Forest plot showed the prevalence of dry mouth in COVID-19 patients.

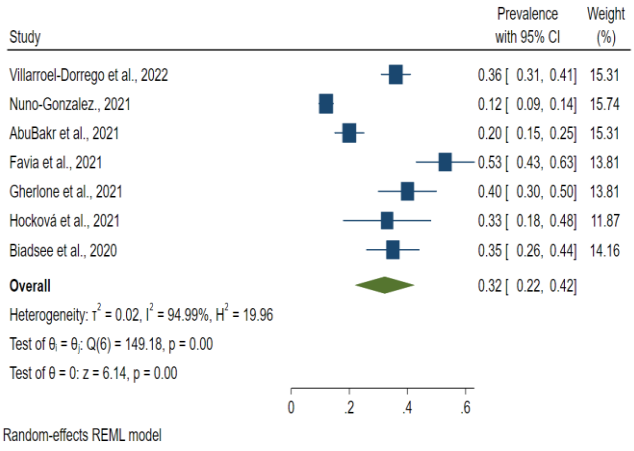

Figure 3. Forest plot showed the prevalence of Oral lesions in patients with COVID-19.

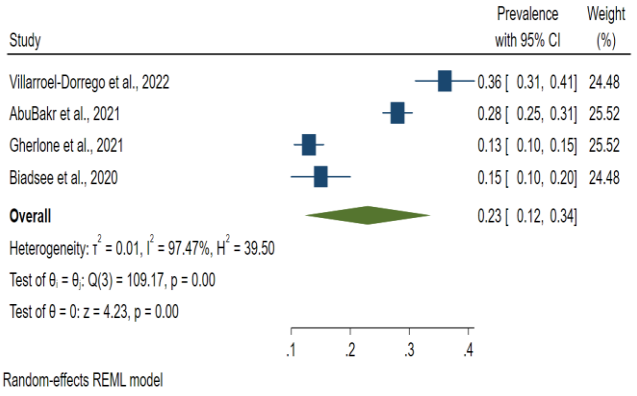

Figure 4. Forest plot showed the prevalence of Orofacial pain in patients with COVID-19.

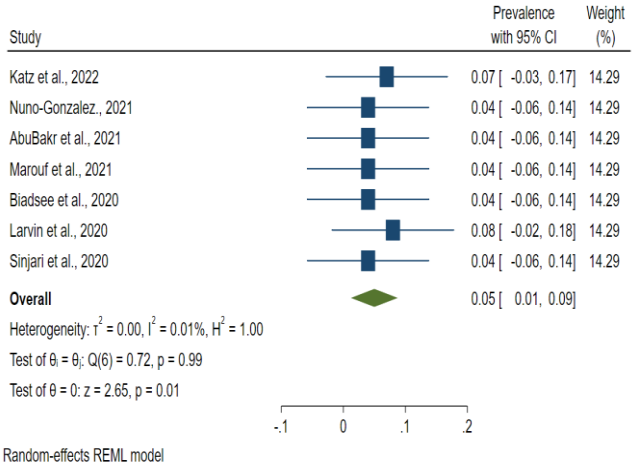

Figure 5. Forest plot showed the prevalence of Periodontal diseases in patients with COVID-19.

Discussion

In the present study, an effort was made to investigate the relationship between COVID-19 and oral health conditions. Accordingly, the meta-analysis showed that the prevalence of dry mouth was more reported in patients with COVID-19, followed by Oral lesions in a high percentage of patients. However, there is a high heterogeneity between studies, which can be due to geographical conditions and variables such as age and gender. In terms of orofacial pain, the prevalence is reported to be 23%, which should be evaluated in COVID-19 patients. On the other hand, the lowest prevalence was associated with periodontal disease, and in 5% of patients with periodontal disease, COVID-19 disease is observed. These findings indicate that oral hygiene is very important in preventing COVID-19. Research shows a statistically significant relationship between COVID-19 and periodontal symptoms, but there is no significant relationship regarding increased mortality. Because in the selected studies, there was a large heterogeneity between the studies in terms of severity and mortality, and in a few studies, this relationship was mentioned; these variables were not

included in the meta-analysis. According to the available literature, dry mouth and periodontal symptoms are very common in COVID-19 patients. [5, 15, 21, 23] These findings may be that ACE-2 receptors in the oral cavity allow the virus to multiply and can affect the process of destruction and inflammation of oral tissue.[27] According to studies, the oral cavity may be susceptible to COVID-19 infection because the epithelial cells of the oral mucosa have ACE2 and TMPRSS2 receptors, which may promote this process.[28] According to Fernandes Matuck et al., 2021, in patients with COVID-19, the presence of SARS-CoV-2 in periodontal tissue was confirmed.[29] It has also been reported that ACE2 receptors can determine the course of SARS-CoV-2 infection and cause dysfunction. Evidence shows that people with good oral health have a much lower incidence of COVID-19 than people with poor oral health.[30] Some studies have reported that associated manifestations of antibiotic therapy or poor immunity can also affect oral health conditions.[31] In a study, a questionnaire about the oral and dental health status of patients with covid-19 was used to evaluate oral manifestations; 108 patients, 52 men, and 56 women, were examined, and the oral manifestations of COVID-19 included loss of taste (47.2%), dry mouth (46.3%), dryness and inflammation of the mouth (11.1%). According to the findings of the study, Patients with COVID-19 frequently experience oral symptoms like dry mouth and taste loss, which could be part of the COVID-19 diagnostic criteria.[32] According to research, oral manifestations of COVID-19 included dry mouth, taste problems, a burning sensation, and trouble swallowing in 20% of patients, and 30% of them had dry mouth during hospitalization.[33] COVID-19 is one of the important issues that has been of interest in many different medical fields, and experts are trying to create appropriate management standards depending on the clinical situation. Therefore, investigating the prevalence of symptoms related to the disease can help properly treat patients with chronic diseases in a new epidemic reality. Therefore, antibiotic treatment may also predispose patients to oral health conditions and increase the prevalence of dry mouth. These findings are very challenging, and more extensive studies are needed in this area in order to provide stronger evidence in this area.[5] It is suggested that further studies be performed considering the relationship between COVID-19 and the effect of the inflammatory response on oral homeostasis, as well as studies investigating the effect of antibiotics and other drug therapies used to treat COVID-19 on oral health conditions. One of the limitations of the present study was that there is a high heterogeneity between studies. The reason can be the study design, non-probability sampling, and non-comparison with the control group. The follow-up period should also be considered in the studies in order to provide stronger results. On the other hand, there is a direct relationship between a weak immune system and periodontal symptoms, which may be related to the prevalence of periodontal symptoms associated with a weakened immune system. Also, the relationship between age and gender with oral conditions and their relationship with COVID-19 should be considered because it can be considered a factor in increasing the prevalence. The association between underlying diseases, oral conditions, and COVID-19 should also be thoroughly investigated.

Conclusions

Based on the findings of the present meta-analysis, the prevalence of dry mouth in patients with COVID-19 was higher than in oral lesions and orofacial pain; It also had the lowest prevalence associated with periodontal symptoms. Although a low prevalence is observed for periodontal symptoms, it is directly related to the severity of COVID-19 disease. These findings indicate that oral hygiene can slow the progression of the disease or prevent COVID-19. Of course, it should be noted that to confirm the findings of the present study. There is a knowledge gap and heterogeneity between the above studies; more studies and more research should be done. Finally, future studies must focus on the relationship between COVID-19 and oral health conditions, as well as factors such as age, gender, the effect of the inflammatory response on oral homeostasis, and medication.

Conflict of Interest

The authors declared that there is no conflict of interest.

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