Evaluation of the potential for transmission of coronavirus disease via saliva: a systematic review and meta-analysis

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Aim: One of the main factors that play a pivotal role in the transmission of COVID-19 from human to human is saliva; according to the subject's importance, the present study aimed to evaluate the potential of transmission via the saliva of coronavirus disease. Methods: PubMed, ISI, Embase, Scopus, Medicine have been used until September 2020 to search for articles. Therefore, EndNote X9 used to manage electronic resources. A 95% confidence interval (CI) effect size, fixed effect model, inverse-variance methods have been calculated. The positive rate of SARS-CoV2 assessed with meta analysis. To deal with potential heterogeneity, random effects were used, and I² showed heterogeneity. I² values above 50% signified moderate-to-high heterogeneity. The Meta-analysis has been evaluated with Stata/MP v.16 (the fastest version of Stata) statistical software. Results: According to the study’s purpose, in the initial search with keywords, 19 articles were found, the full text of 3 studies was reviewed, and finally, three studies were selected. The positive rate of SARS-CoV2 was 86% (86%; 95% CI 67 %-100%). Conclusion: saliva can be a non-invasive specimen type for diagnosis of COVID-19. Dentists should be aware that saliva plays a major role in the transmission of COVID-19 from human to human, and failure to follow prevention protocols can contaminate them.

Keywords: COVID-19. Dental health services. Saliva.

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Received: December 12, 2020
Accepted: December 29, 2020
Introduction

In the current context of the world, since the advent of COVID-19 in December 2019 in Wuhan, China, the disease has become a major global health concern. On February 11, 2020, The World Health Organization (WHO) has declared a new title for the 2019-nCoV: Corona Virus Disease (COVID-19) epidemic infection. According to the WHO, the global mortality rate over time was estimated at 5.7% using a 14-day estimate. Early studies reported transmitted from animals to humans, but studies have illustrated human-to-human transmission of the covid-19 through droplets or direct contact. So far, the 2019-nCoV has affected more than 43,150,456 reported cases, according to a new report by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) (October 26, 2020). In the sixth edition of the COVID-19 treatment regimen (Trial Implementation), it was reported that the possible routes of transmission of COVID-19 are direct contact and transmission through respiratory particles. In a closed environment, aerosols may be transferred, and more people are at risk for aerosol transmission. COVID-19 transmission is expected to be seen during contact during dental clinical procedures with droplets and aerosols; aerosols can pose potential risks to the dentist and reciprocally to the patient. Dentists need to evaluate effective strategies to prevent COVID-19 infection during the aerosol production process. One of the main factors that play a pivotal role in the transmission of COVID-19 from human to human is saliva. According to the subject’s importance, the present study aimed to evaluate the effect size of 2019-nCoV and the potential of transmission via the saliva of coronavirus disease.

Materials and Methods

PubMed, ISI, Embase, Scopus, Medicine have been used until September 2020 to search for articles. Therefore, EndNote X9 is used to manage electronic resources. PubMed search was conducted using mesh terms:

("COVID-19 vaccine" [Supplementary Concept] OR "COVID-19 diagnostic testing" [Supplementary Concept] OR "COVID-19" [Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept]) AND ("Saliva"[Mesh] OR "saliva-interacting cell wall protein, Streptococcus" [Supplementary Concept] OR "saliva natura" [Supplementary Concept]) AND "Dental Health Services"[Mesh].

The present study answers the following question:

What is the probability of transmitting the coronavirus disease through saliva?

Inclusion criteria included were randomized controlled trials studies, controlled clinical trials, In vitro studies, case studies, case reports, and prospective and retrospective cohort studies. Only studies have reported the transmission of COVID-19 through saliva and saliva specimens were collected at 0–14 days after hospitalization. Review studies were excluded from the present article.
Data extraction methods

Data extracted from the studies were included sample size, study, study design. Newcastle-Ottawa Scale (NOS) used to assessed quality of the cohort studies, The scale scores range from 0 (lowest grade) to 6 (highest grade). Effect size with 95% confidence interval (CI), fixed effect model, Inverse-variance methods were calculated. To deal with potential heterogeneity, random effects were used, and I^2 showed heterogeneity. I^2 values above 50% signified moderate-to-high heterogeneity. The Meta-analysis has been evaluated with Stata/MP v.16 (the fastest version of Stata) statistical software.

Results

According to the study’s purpose, in the initial search with keywords, 19 articles were found. In the first step of selecting studies, 14 studies were selected to review the abstracts. Then, studies that did not meet the inclusion criteria were excluded from the study. In the second step, the full text of the three studies was reviewed. Finally, three studies were selected (Figure 1).

Characteristics

The sample size total was 74 patients with 62 years mean of age between 37-75 years. Saliva specimens in To et al. (2020)\textsuperscript{8}, Meng et al.\textsuperscript{9} (2020) and Williams et al. (2020)\textsuperscript{10}
were 2, 4 and 6 days, respectively. Overall, 11/12, 20/23, and 33/39 patients detected in saliva in To et al. (2020), Meng et al. (2020) and Williams et al. (2020), respectively.

The positive rate of SARS-CoV2

The effect size of studies included in the present systematic review and meta-analysis was 86% (86%, 95% CI 69%–100%). This result has shown saliva’s potential to be a non-invasive type of specimen for 2019-nCoV diagnosis and viral load monitoring.

### Table 1. Details of selected studies according to inclusion criteria

| Study. Years | Study design | Place | Sample size | Mean/Range of age (years) | Patient specimens | Saliva specimens* | SARS-CoV-2 detected in saliva |
|--------------|--------------|-------|-------------|--------------------------|------------------|------------------|-----------------------------|
| To et al., 2020 | Cohort       | public Health Laboratory Services Branch in Hong Kong | 12 Female:5 Male:7 | 62.5/37 to 75 | 2 mL Saliva / cough sterile | Two days 0-7 days | 11/12 |
| Meng et al., 2020 | Cohort      | Hospital of Stomatology, Wuhan University | 23 Female:10 Male:13 | 62 / 37–75 | ----- | Four days 0-13 days | 20/23 |
| Williams et al., 2020 | Cohort  | Royal Melbourne Hospital | 39 NR NR | six days 0-14 days | 33/39 |

* Saliva specimens were collected at a median of days after hospitalization

### Figure 2. Forest plot showed an effect size of 2019-nCoV was detected in the initial saliva specimens.

**Discussion**

The most common symptoms are: fever, tiredness, cough, aches and pains, sore throat, conjunctivitis, diarrhea, loss of taste or smell, headache, skin rash, or finger or toe discoloration are less common symptoms. And most importantly, there are Severe symptoms require special attention, which includes: shortness of breath
or difficulty breathing, chest pain or pressure, loss of speech or movement\textsuperscript{11,12}. Although coronavirus infection is mild, severe acute respiratory syndrome coronavirus (SARS-CoV) leads to high mortality rates\textsuperscript{13}. It should be noted that some patients are carriers and have only mild symptoms (carriers). It takes an average of 5-6 days for a person to get the virus to show symptoms, but it can take up to 14 days. Some of the characteristics of the virus are still unknown due to the novelty of the virus. COVID-19 has recently been reported to be detected in infected patients’ saliva, so its spread through saliva is possible. Casaroto et al.\textsuperscript{13}, 2020, evaluate the effect of cooling water temperatures on changes in pulp chamber temperatures and showed when using a high-speed handpiece, too much heat is generated, which should use a water coolant. Water coolant can create aerosols, and when combined with saliva in the oral cavity, bio-aerosols are formed. Bio-aerosols originate from various sources and may be hazardous to healthcare workers and patients due to their potential pathogenic nature. Zemouri et al.\textsuperscript{14}, 2017, in a review reported that 38 types of microorganisms found in the dental clinic air, and for both patients and healthcare workers, all aerosols may be hazardous. Several studies show that the transmission of Covid-19 occurs mostly through oral droplets\textsuperscript{15-18}.

Studies in the field of oral dentistry provide an opportunity to determine if a diagnosis of non-invasive saliva for COVID-19 could assist detect such viruses and reduce their spread. In China, researchers can develop unique PCR tests focusing on COVID-19 diagnosis by examining viral genome sequence data from international GenBank databases\textsuperscript{12,19}. To date, the routes of transmission of COVID-19 have not been fully elucidated; however, human-to-human transmission has been confirmed. Throat samples and blood tests can be used to diagnose the virus\textsuperscript{20-22}.

Potential routes of transmission of COVID-19 include Cough, sneezing, and aerosols produced during the clinical process and even talking. As a result, it can be said that the source of the droplets can be the throat or pharyngeal cavity, which are generally associated with saliva\textsuperscript{23}. Small droplets can remain suspended in the air, and larger droplets can help transmit the virus. It has also been reported that transmission by contaminated blood may occur. Dentists may carelessly or unknowingly care for carrier patients\textsuperscript{21,24}. Studies have shown that about 29% of patients with COVID-19 are health care workers\textsuperscript{25}.

Because the airborne particles and aerosols produced during the dental process are inhaled, COVID-19 transmission occurs rapidly in dentistry, especially in dentists who directly contact the patient\textsuperscript{26}. As a result, dentists should be aware of prevention methods and adopt preventive strategies. According to the mentioned transmission routes, COVID-19 can spread to dental offices. As a result, hands should be washed regularly, all equipment and surfaces should be disinfected regularly, and personal protective equipment and preferably disposable items should be used. Aerosol droplets are produced when coughing, laughing, talking, or sneezing. Aerosol droplets are droplets smaller than five \textmu{}m diameter and larger droplets larger than 5 \textmu{}m diameter. Small droplets settle faster than larger droplets and stay in the air longer, while large droplets fall to the ground quickly and can be transferred to another person in less time\textsuperscript{27}. Otter et al.\textsuperscript{28}, 2013 evaluate the evidence that contaminated surfaces contribute to the transmission of pathogens.
in hospitals; the result showed contaminated surfaces contribute to transmission. Baghizadeh Fini. 29, 2020, examine the routes of respiratory virus transmission among humans; the result showed respiratory viruses, droplets, or aerosols are transmitted via contact.

One way to diagnose COVID-19 is to use salivary diagnosis platforms, which may detect saliva infection in some virus strains for up to 29 days. In this type of test, because the person has close contact with infected patients to collect the sample, there may be a transmission risk.

The COVID-19 virus is present in saliva in three different pathways:

1. Lower or upper respiratory tract presence
2. Enter with fluids
3. Minor or major salivary gland infection

In an animal study, it was shown that salivary gland cells could be the main source of COVID-19. Further studies on saliva and its effect on the transmission of the virus should be performed to confirm these findings. To suggest more effective follow-up methods, especially in dentists who perform aerosol production methods themselves.

The current systematic review and meta-analysis have aimed to evaluate the potential of transmission via the saliva of coronavirus disease. Present meta-analysis showed overall 86% patients (86%; 95% CI 67 %-100%) had SARS-CoV-2 detected in saliva. Personal protective equipment and hand cleanliness practices, Personal protective equipment (PPE), preprocedural mouth rinse, Single-Use (Disposable), periapical radiography. Cone-beam computed tomography (CBCT) and periapical (PA), Rubber dam, sodium hypochlorite for root canal irrigation, disinfect inanimate surfaces, Ultrasonic scaling instruments and, airborne Infection Isolation.

The advantages of using saliva samples in the diagnosis of 2019-nCoV can be the following:

1. Saliva samples can be easily prepared by the patient without any invasive methods.
2. The use of saliva samples can reduce the risk of nosocomial transmission 2019-nCoV.
3. Saliva samples can be collected in outpatient or community clinics.
4. In an environment where large numbers of people need screening, saliva is a non-invasive sample.
5. Using saliva samples reduces the waiting time to collect samples, so results will be available faster. This method is especially important in crowded hospitals where the number of available staff is limited.

The results of the present systematic review and meta-analysis study show that saliva can be a non-invasive type of specimen used to diagnose COVID-19. Saliva can be easily obtained from the patient, saliva use also reduces the risk of transmission, and
saliva samples can be useful for patients who cannot be PCRed. Salivary transmission is also possible and should be observed in dental clinics so that patients are not exposed to saliva. Finally, all dentists should be aware that saliva plays a major role in the transmission of COVID-19 from human to human, and failure to follow prevention protocols can contaminate them.

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