Review article

Comparing saliva and nasopharyngeal swab specimens in the detection of COVID-19: A systematic review and meta-analysis

Kaveh Nasiri a*, Aleksandra Dimitrova b

a Essen, Germany
b Department of Hematology, Internal Oncology & Stem Cell Transplant, Evang Hospital, Essen-Werden, Essen, Germany

Received 23 November 2020; Final revision received 17 January 2021
Available online 29 January 2021

KEYWORDS
COVID-19; Meta-analysis; Nasopharyngeal swab; Saliva

Abstract  Background/purpose: Due to the easy transmission of COVID-19, the virus is a threat to global health. Early diagnosis of suspected patients will play an essential role in preventing further spread of COVID-19. The aim of this review study was to evaluate saliva specimen in comparison to nasopharyngeal swab (NPS) specimen in studies selected from various databases.

Materials and methods: To achieve the objective of this study, a systematic literature search was carried out in four databases, namely PubMed, Google Scholar, Cochrane Library, and LILACS. The keywords “COVID-19”, “Nasopharyngeal Swab”, and “Saliva” were utilized via Boolean operators.

Results: 14 articles were included in this review study following the eligibility criteria. Based on data presented in studies used in the meta-analysis, there was no significant difference between both specimen types for detection of COVID-19. Heterogeneity test showed that I² value was 5.790% (<20%). The effect size (risk ratio) of the 14 studies was 0.951 (<1).

Conclusion: With the results revealing no significant difference between the two types of specimen in the diagnosis of COVID-19, the use of saliva specimen is preferable for widespread use because it is easily collected without the need for qualified health workers. However, more in vivo studies are required in order to compare and evaluate saliva and NPS specimens in detecting COVID-19 using various techniques.

© 2021 Association for Dental Sciences of the Republic of China. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Introduction

The outbreak of a respiratory virus with unclear origin began in December 2019, in Hubei province, China, and soon posed a threat to global health due to its easy transmission. After extensive research on the virus, it was categorized as a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Later, in February 2020, the World Health Organization (WHO) named the virus “Corona Virus Diseases 2019” (COVID-19). To control the fast spread of the virus, various measures including social distancing and lockdowns were taken in many parts of the world, disrupting the living and working conditions of people.

It is essential to find a safe and reliable diagnostic specimen type and its potential implication for detecting COVID-19, particularly in asymptomatic patients. SARS-CoV-2 has been detected in different specimens of human body, including saliva, nasopharyngeal or oropharyngeal swabs, blood, feces, urine, and tears, among which nasopharyngeal swab and saliva are more commonly used for the detection of COVID-19. Nonetheless, nasopharyngeal swabbing followed by real-time reverse transcription polymerase chain reaction (RT-PCR) technique is the best choice for detection of COVID-19. Nonetheless, the collection of NPS specimen can cause the patient to cough, or bleed (especially in patients with thrombocytopenia), increasing the risk of transmitting the virus to healthcare workers. On the contrary, collecting saliva specimen decreases the possibility of exposing healthcare personnel to COVID-19 as it can be self-collected through spitting into a sterile bottle. Thus, saliva specimen can be used as an alternative for the detection of COVID-19. Saliva is secreted by salivary glands and consists of proteins, peptides, and other molecular compounds which have various biological functions in the oral cavity. Saliva is considered as a diagnostic window for various pathologies diseases, particularly respiratory viruses such as COVID-19. The aim of this review study was to evaluate saliva and NPS specimens in detecting COVID-19 using RT-PCR.

Material and methods

Literature search

Electronic literature search was carried out across PubMed, Cochrane Library, Google Scholar, and LILACS to find intended articles published from December 2019 to October 2020. The Boolean operators “AND” and “OR” were utilized for the following search keywords: COVID-19, nasopharyngeal swab, and saliva in various combinations. The search results were collected and imported into the reference manager of EndNote Software and duplicate papers were eliminated. It should be added that the data extraction was performed by two investigators.

PICO question is as follows:

Is the saliva sample a reliable diagnostic method (I) for the detection of COVID-19 (O) in patients (P) compared to the nasopharyngeal swab sample (C)?

Population: Patients.

Intervention: Saliva specimen.

Comparison: Nasopharyngeal swab specimen.

Outcome: Detection of COVID-19.

Inclusion criteria

The criteria for the inclusion of articles in this literature review:

1. Full text of articles written in English.
2. All papers published from December 2019 to October 2020.
3. In vivo studies.
4. Studies on the comparison between saliva (posterior saliva) and nasopharyngeal swab specimens for detecting COVID-19; the presence or absence of other specimens are not essential.

Exclusion criteria

The criteria for the exclusion of articles in this literature review:

1. Review studies.
2. Studies with unclear data.
3. Studies with no main results, including guidelines and recommendations.

Results

The initial search yielded 940 articles. After the removal of duplicates, 926 articles were screened by title, as a result of which 860 articles were excluded because they did not include a comparison between saliva and nasopharyngeal swab specimens. At the next stage, the abstracts of the remaining 66 articles were assessed, which resulted in the exclusion of 42 more articles for two reasons; 1. The studies focused on various diagnostic techniques rather than the efficacy of specimen types in detecting the virus. 2. The studies contained unclear data with regard to either the results or participants. It should be mentioned that out of the 66 articles, 7 articles were not accompanied with an abstract, so to examine them, the full texts were reviewed directly. Thus, 24 articles were included for the full-text review; in this process, 7 articles were discarded since they addressed a different PICO question or did not clearly answer the question. Further, in one article, the patients’ participation was considerably higher than that of other studies, which led to an intervention in the analysis. And the other article showed no clear data in the final test. Also, the full text of one study was not available despite contacting the authors and requesting the full text. Therefore, at the end of the screening process, 14 articles met all the criteria and were included in the quantitative analysis.

Fig. 1 depicts the study selection process. Table 1 and Fig. 2 provide general information on the selected articles. It needs to be clarified that in the studies by Jamal et al. and Williams et al., T (total number of patients participating in the study) in the meta-analysis and data visualisation is, in fact, the number of the participating
patients which were considered in the final analysis for detection of COVID-19.\textsuperscript{9,14} In addition, due to unclear data on 8 patients in the study by Procop et al., 8 specimens were excluded from the final comparative analysis; therefore, the rest of participating patients were included in the meta-analysis and Fig. 2.\textsuperscript{16}

Statistical heterogeneity test was assessed using the $I^2$ statistics. $I^2$ value showed 5.79% ($<20\%$). P-value was 0.09 which is less than 0.1 (10%) and indicates that heterogeneity at 90% confidence interval was not statistically significant. Fig. 3 presents 14 included studies in the meta-analysis in which the risk ratio was selected as the effect size. The total effect size was 0.951 ($<1$), which means that based on data presented in studies used in the meta-analysis, saliva and NPS specimens had the same precision in detecting COVID-19.

Fig. 4 illustrates forest plot graphic representation of the results of the meta-analysis. Studies were grouped into two categories, namely group N (nasopharyngeal swab specimen) and group S (saliva specimen). Group N consists of the studies in which the number of patients that tested positive using NPS specimens was greater than the number...
of patients that tested positive using saliva specimens. In contrast to group N, group S consists of the studies in which the number of patients that tested positive using saliva specimens was more than those tested using NPS specimens.

The overall risk ratio of group N and group S were 0.898 and 1.109, respectively. While the overall risk ratio for both groups (0.898 and 1.109) was nearly the same, the 95% confidence interval half width for group S (0.135) was nearly twice as group N (0.065). Therefore, it could be concluded that the dispersion in studies categorized as group S is greater than those categorized as group N. Since events and total data of the study by Iwasaki et al. were the same, the study was not included in the forest plot of meta-analysis in Fig. 4.

### Discussion

Real Time Polymerase Chain Reaction (RT-PCR) is the gold standard for the detection of SARS-CoV-2 infection from various clinical specimens. However, the sensitivity and specificity of different RT-PCR kits are not 100% accurate. Many factors can affect the results, including the collection procedure, handling of material, and viral load of the sample (e.g., duration of symptoms and severity of disease). The range of reported agreement or disagreement between saliva and NPS specimens as diagnostic specimen types in the detection of COVID-19 is different in studies. Hence, this study aimed to compare saliva specimen with NPS specimen to identify which specimen type is reliable for the diagnosis of COVID-19. To do so, meta-analysis was employed to reach a comprehensive conclusion.

The use of saliva as a diagnostic tool for the detection of RNA viruses, such as ZIKA and Ebola viruses is well established. Findings of previous studies reported satisfactory outcomes in the detection of SARS-CoV-1/2 RNA using saliva specimens. Saliva specimen requires preparation prior to RNA extraction and getting the right volume is essential. On the contrary, swabbing of the nasopharynx is done through the nasal cavity via palpation without direct visualization, which if performed incorrectly can lead to an increased false-negative result. Therefore, knowledge of the anatomy of the nasal cavity is essential for the health care personnel who perform this procedure.

Quantitative analysis in the present review study revealed the same effect size for saliva and NPS specimens in detecting COVID-19 using RT-PCR, indicating that they can both detect the virus reliably. This finding is in agreement with that of previous studies. Since both specimens have similar detection rate, the simplicity of the sample collection would be highlighted, meaning saliva sampling is not only easier but also safer. Moreover, the presence of trained healthcare workers to collect saliva specimen is not required. To answer the PICO question, there is no significant difference between saliva and NPS specimens in detecting COVID-19 using RT-PCR technique. Nonetheless, using saliva specimen seems to be the better option due to its convenient and fast collecting.

The result of the viral culture of group S in Fig. 4 demonstrated that the viral load of SARS-CoV-2 was higher in salivary samples, which may be due to the fact that ACE-2 cells that cover the salivary gland ducts are the first target of SARS-CoV. Hence, the viral load of SARS-CoV-2 might be higher in the salivary gland than in the nasopharynx. However, meta-analysis revealed that neither saliva nor NPS specimens are 100% sensitive in detecting COVID-19. It is suggested that in order to confirm diagnosis in suspected cases with a negative COVID-19 result, a combination of saliva and NPS specimens should be used.

In contrast to other review studies concerning SARS-CoV-2 which included only 5, 7, and 11 articles in the quantitative synthesis, our study utilized 14 articles to support the result and ensure a firm conclusion between saliva and NPS specimens in detecting COVID-19. Moreover, since there is still limited data on COVID-19, this review study did not take other factors, such as other specimens and severity of disease or others diagnostic techniques into account. Further studies should address these issues.
Figure 2  Data visualisation of selected studies.

Figure 3  Blobbogram results of meta-analysis among 14 studies.
Based on the findings of this study, it can be concluded that the overall concordance of saliva and NPS specimens is the same for the detection of SARS-CoV-2 RNA using RT-PCR. However, saliva is suggested to be used as a non-invasive specimen providing satisfactory results in detecting COVID-19. Nonetheless, more data are needed to evaluate the sensitivity of saliva and NPS specimens in suspected patients.

References

1. Nasiri K. COVID-19 and the antiviral effect of saliva. Eur J Dermatol 2020;14:5177–8.
2. Esakandari H, Nabi-Afjadi M, Fakkari-Afjadi J, Farahmandian N, Miresmaeli SM, Bahreini E. A comprehensive review of COVID-19 characteristics. Biol Proced Online 2020; 22:19.
3. Fang Z, Zhang Y, Hang C, Ai J, Li S, Zhang W. Comparisons of viral shedding time of SARS-CoV-2 of different samples in ICU and non-ICU patients. J Infect 2020;81:147–78.
4. Altawahah H, AlHuraish F, Alkandari WA, Ezizkouri S. Saliva specimens for detection of severe acute respiratory syndrome coronavirus 2 in Kuwait: a cross-sectional study. J Clin Virol 2020;132:104652.
5. Kim YG, Yun SG, Kim MY, et al. Comparison between saliva and nasopharyngeal swab specimens for detection of respiratory viruses by multiplex reverse transcription-PCR. J Clin Microbiol 2016;55:226–33.
6. To KK, Tsang OT, Yip CC, et al. Consistent detection of 2019 novel coronavirus in saliva. Clin Infect Dis 2020;71:841–3.
7. Nasiri K. Human saliva as an effective sample for the detection of COVID-19. Dent Oral Maxillofac Res 2020;6:1–2.
8. Chen JH, Yip CC, Poon RW, et al. Evaluating the use of posterior oropharyngeal saliva in a point-of-care assay for the detection of SARS-CoV-2. Emerg Microb Infect 2020;9:1356–9.
9. Jamal AJ, Mozafarshahjin M, Coomes E, et al. Sensitivity of nasopharyngeal swabs and saliva for the detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis 2020. https://doi.org/10.1093/cid/ciaa848.
10. Kandel C, Zheng J, McCready J, et al. Detection of SARS-CoV-2 from saliva as compared to nasopharyngeal swabs in outpatients. Viruses 2020;12:1314.
11. Landry ML, Criscuolo J, Peaper DR. Challenges in use of saliva for detection of SARS CoV-2 RNA in symptomatic outpatients. J Clin Virol 2020;130:104567.
12. Pasomsub E, Watcharananan SP, Boonyawat K, et al. Saliva sample as a non-invasive specimen for the diagnosis of coronavirus disease 2019: a cross-sectional study. Clin Microbiol Infect 2020. https://doi.org/10.1016/j.cmi.2020.05.001.
13. Vaz SN, Santana DS, Netto EM, et al. Saliva is a reliable, non-invasive specimen for SARS-CoV-2 detection. Braz J Infect Dis 2020;24:422–7.
14. Williams E, Bond K, Zhang B, Putland M, Williamson DA. Saliva as a noninvasive specimen for detection of SARS-CoV-2. J Clin Microbiol 2020;58.
15. Leung EC, Chow VC, Lee MK, Lai RW. Deep throat saliva as an alternative diagnostic specimen type for the detection of SARS-CoV-2. J Med Virol 2020. https://doi.org/10.1002/jmv.26258.
16. Procop GW, Shrestha NK, Vogel S, et al. A direct comparison of enhanced saliva to nasopharyngeal swab for the detection of SARS-CoV-2 in symptomatic patients. J Clin Microbiol 2020;58.
17. Senok A, Alsuwaidi H, Atrah Y, et al. Saliva as an alternative specimen for molecular COVID-19 testing in community settings and population-based screening. Infect Drug Resist 2020;13:3393–9.
18. Wyllie AL, Fournier J, Casanovas-Massana A, et al. Saliva or nasopharyngeal swab specimens for detection of SARS-CoV-2. N Engl J Med 2020;383:1283–6.
20. Yokota I, Hattori T, Shane PY, et al. Equivalent SARS-CoV-2 viral loads between nasopharyngeal swab and saliva in symptomatic patients. medRxiv 2020. https://doi.org/10.1101/2020.09.01.20186254.

21. Iwasaki S, Fujisawa S, Nakakubo S, et al. Comparison of SARS-CoV-2 detection in nasopharyngeal swab and saliva. J Infect 2020;81:e145–7.

22. Younes N, Al-Sadeq DW, Al-Jighefee H, et al. Challenges in laboratory diagnosis of the novel coronavirus SARS-CoV-2. Viruses 2020;12:582.

23. Goudouris ES. Laboratory diagnosis of COVID-19. J Pediatr 2020;97:7–12.

24. Watson J, Whiting PF, Brush JE. Interpreting a COVID-19 test result. BMJ 2020;369:m1808.

25. Yoon JG, Yoon J, Song JY, et al. Clinical significance of a high SARS-CoV-2 viral load in the saliva. J Kor Med Sci 2020;35:e195.

26. Azzi L, Carcano G, Gianfagna F, et al. Saliva is a reliable tool to detect SARS-CoV-2. J Infect 2020;81:45–50.

27. Rao M, Rashid FA, Sabri FSAH, et al. Comparing nasopharyngeal swab and early morning saliva for the identification of SARS-CoV-2. Clin Infect Dis 2020. https://doi.org/10.1093/cid/ciaa1156.

28. Khurshid Z, Zafar M, Khan E, Mali M, Latif M. Human saliva can be a diagnostic tool for Zika virus detection. J Infect Public Health 2019;12:601–4.

29. Niedrig M, Patel P, El Wahed AA, Schädler R, Yactayo S. Find the right sample: a study on the versatility of saliva and urine samples for the diagnosis of emerging viruses. BMC Infect Dis 2018;18:707.

30. Zhu J, Guo J, Xu Y, Chen X. Viral dynamics of SARS-CoV-2 in saliva from infected patients. J Infect 2020;81:48–50.

31. Wang WK, Chen SY, Liu U, et al. Detection of SARS-associated coronavirus in throat wash and saliva in early diagnosis. Emerg Infect Dis 2004;10:1213–9.

32. Kaufman AC, Brewster R, Rajasekaran K. How to perform a nasopharyngeal swab - an otolaryngology perspective. Am J Med 2020;133:1280–2.

33. Fakheran O, Dehghannejad M, Khademi A. Saliva as a diagnostic specimen for detection of SARS-CoV-2 in suspected patients: a scoping review. Infect Dis Poverty 2020;9:100.

34. Czumbel LM, Kiss S, Farkas N, et al. Saliva as a candidate for COVID-19 diagnostic testing: a meta-analysis. Front Med 2020;7:465.

35. Bwire GM, Majigo MV, Njiro BJ, Mawazo A. Detection profile of SARS-CoV-2 using RT-PCR in different types of clinical specimens: a systematic review and meta-analysis. J Med Virol 2021;93:719–25.

36. Mohammadi A, Esmaeilzadeh E, Li Y, Bosch RJ, Li JZ. SARS-CoV-2 detection in different respiratory sites: a systematic review and meta-analysis. EBioMedicine 2020;59:102903.