Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Is saliva collected passively without forceful coughing sensitive to detect SARS-CoV-2 in ambulatory cases? A systematic review

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Objective. This systematic review was conducted to assess the sensitivity rate of SARS-CoV-2 detection in the saliva of ambulatory asymptomatic and mildly symptomatic patients, with saliva being collected passively without any forceful coughing.

Study Design. A literature search was performed from January 2020 to July 2021. Prospective studies excluding letters to editors were included in our review only if saliva and nasopharyngeal samples were collected simultaneously and sensitivity was reported using reverse transcription polymerase chain reaction (RT-PCR) in asymptomatic or mildly symptomatic ambulatory cases.

Results. A total of 436 studies were assessed; 10 (4 cohorts and 6 cross-sectional) studies met our inclusion criteria. The sensitivity rate of saliva to detect SARS-CoV-2 varied from 85.7% to 98.6% in all except for 3 studies. Lower sensitivity levels were attributed to low viral load (51.9% and 63.8%) or lack of supervision while collecting saliva (66.7%).

Conclusions. Passively collected saliva in the absence of coughing has a high sensitivity rate to detect SARS-CoV-2 in asymptomatic and mildly symptomatic patients compared with nasopharyngeal swabs. Limitations of previous studies, such as lack of attention to the method of saliva collection, stages, and severity of the disease at the time of sample collection, can be researched in future investigations. (Oral Surg Oral Med Oral Pathol Oral Radiol 2022;133:530−538)

The COVID-19 pandemic has had a catastrophic effect on different parts of the world, resulting in more than 4 million deaths worldwide as of August 2021. In the United States, more than 700,000 deaths have occurred due to SARS-CoV-2 infection.[1] Since the start of the pandemic, the American Dental Association (ADA) and the Centers for Disease Control and Prevention (CDC) have continually provided practice guidelines for dentists.[2,3] With a nationwide vaccination program, oral health care providers, like most people in the United States, were hoping for the end of this pandemic; however, with the data showing that not everyone has been vaccinated, and with resurges we are experiencing due to the emergence of mutant variants, it seems that we are still away from end of the pandemic. Some studies suggest that the resurgence of COVID-19 could extend into 2024.[4]

Data show that nearly 91% of dentists have provided some type of emergency oral care during the COVID-19 pandemic.[5] The positivity rate of SARS-CoV-2 has been reported in asymptomatic patients attending dental clinics. The range is from 0.6% in the population referred to oral health care centers to 2.3% in pediatric dental clinics.[6,7] Palla et al.[8] reported a higher rate of positivity in asymptomatic patients attending the emergency department, half of whom had visited a dentist within 7 days from their visit. Due to the relatively high positivity rate in asymptomatic cases and the fact that 17.9% to 33.3% of infected patients will remain asymptomatic during the disease (especially in cases of the delta variant), the importance of universal precautions and the significance of accessing a rapid screening and diagnostic test, which can be applicable to diagnose asymptomatic patients, especially in the dental setting, should be emphasized.[8-10]

Since the outbreak of the COVID-19 pandemic, oropharyngeal and/or nasopharyngeal swabs (OPS/NPS) have been commonly used. The reverse transcription polymerase chain reaction (RT-PCR) amplification of viral RNA has been recognized as the gold standard procedure to detect SARS-CoV-2. The swab collection can be performed by a trained health care provider and requires close contact between health care workers and potentially infected patients. The procedure causes discomfort and poses a risk of bleeding in some cases,

Statement of Clinical Relevance

Saliva is a promising fluid in the detection and surveillance of infectious diseases. Saliva collected in the absence of coughing has a high sensitivity rate to detect SARS-CoV-2 in asymptomatic and mildly symptomatic patients compared with nasopharyngeal swabs.

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particularly in patients with bleeding disorders, and it increases the risk of disease transmission.[11]

Saliva-based sampling for SARS-CoV-2 detection via RT-PCR has the potential to address many of the barriers associated with nasopharyngeal (NP) swab sampling. Saliva samples can be collected by individuals themselves, with instruction provided by health care personnel. This reduces exposure to the health care team and reduces the need for personal protective equipment (PPE) during collection. Saliva can be collected in sterile containers, removing the need for swabs. These practical advantages reduce human resource needs and could expand the number of persons who can be tested.[12] In addition, as economic issues such as additional costs for infection control are among the concerns for dental practitioners, saliva testing in dental offices can help by reducing exposure and costs.[13]

Since the beginning of the COVID-19 pandemic, many studies have been published reporting the sensitivity rate of saliva in comparison with NP swabs in the diagnosis of, or screening for, SARS-CoV-2 infection.[14-17] These publications are fast-tracked; consequently, multiple systematic reviews have been published to analyze the constantly reported data.[11,12,18-26] Most published systematic reviews have included all types of patients, such as asymptomatic, mildly symptomatic, and severely symptomatic or hospitalized patients, including those in intensive care units, so those cases were in different stages of the disease at the time of sample collection.[11,18,19,23-26] Furthermore, very few studies have evaluated the sensitivity of saliva in ambulatory patients with no or mild symptoms. In addition, the method of saliva collection (passive drooling vs forceful coughing, spitting, or using an oral swab) has not been reviewed in previous studies.[11,18,21,24] Forceful coughing can lead to contamination of saliva with respiratory secretions, gingival crevicular fluid, and microorganisms and their byproducts, which makes it more challenging to assess the true role of saliva in the detection or diagnosis of SARS-CoV-2 infection.[11] Our systematic review is unique in that it is the first systematic review including only the studies with asymptomatic and mildly symptomatic ambulatory cases, and saliva is collected passively without forceful coughing.

METHODS

Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines[27] were used in preparation of this systematic review. The PICO model was used in formulating our research question and identifying the accuracy of saliva to detect SARS-CoV-2 virus in asymptomatic or mildly symptomatic ambulatory cases:

PICO

Is saliva, collected passively in the absence of forceful coughing, sensitive in detecting

SARS-CoV-2 compared with nasopharyngeal swabs in asymptomatic or mildly symptomatic ambulatory patients?

- Patient population: asymptomatic and mildly symptomatic ambulatory individuals tested for SARS-CoV-2 detection
- Intervention: saliva is collected passively without forceful coughing
- Comparison: nasopharyngeal swab collection
- Outcome: saliva sensitivity rate

Information sources and search strategy

We performed a search from January 2020 to July 2021 using PubMed and Scopus databases. Our search terms combinations were formulated in concordance with our fundamental PICO question as follows: (COVID) OR (COVID-19) OR (SARS-CoV-2) AND (diagnosis) AND (saliva).

Study selection criteria

Inclusion criteria were as follows: Prospective cohort studies and cross-sectional studies published in English between January 1, 2020 and July 30, 2021, performed on mildly symptomatic and/or asymptomatic ambulatory patients; studies that paired samples of NPS and saliva collected at the same time and RT-PCR used to detect SARS-CoV-2 infection; and studies reporting the sensitivity value of saliva in detecting SARS-CoV-2 infection.

Exclusion criteria were as follows: studies that included severely symptomatic, hospitalized patients or nursing home cases; retrospective clinical studies, case reports, unpublished manuscripts, conference abstracts, and letters to editors; studies that did not collect both NPS and saliva samples from each patient or did not collect both samples at the same time; studies that did not report the sensitivity rate of saliva in comparison to NP swabs; and studies that did not use passively collected saliva, or studies in which samples were collected by forceful coughing (Figure 1).

Study selection and data collection

Abstracts of 436 studies and full texts of 69 clinical cohorts and cross-sectional studies were selected through the database search and independently assessed by 2 reviewers (A.A. and S.D.); a third reviewer (M.N.) commented to overcome any possible disagreement. A total number of 10 clinical studies were selected based on previously stated inclusion and exclusion criteria. Data were extracted independently

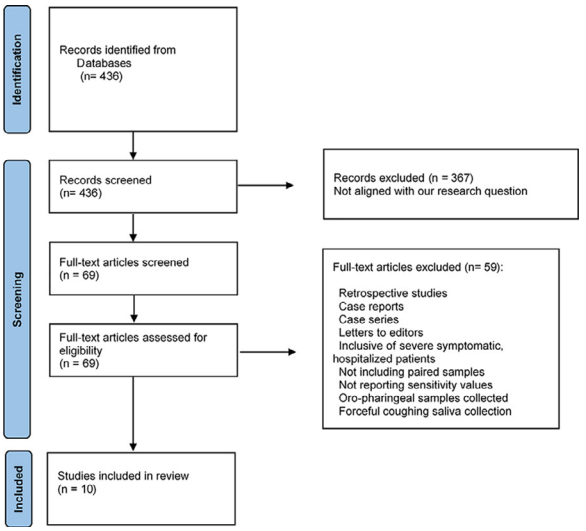

Fig. 1. Study selection process.

by 2 reviewers using full-text articles of selected studies. Collected data included study design, country of origin, sample size, mean age of cases, saliva sample collection instructions, and saliva sensitivity rate.

Quality assessment

The revised Quality Assessment of Diagnostic Accuracy Studies tool[28] was used to assess the quality of selected studies. The risk of bias was assessed in 4 categories: "Patient Selection," "Index Test," "Reference Standard," and "Flow and Timing." Applicability was evaluated in the first 3 of those categories (Figure 2).

RESULTS

A total of 436 papers were obtained through our initial database search; upon review of those abstracts, 69 papers entered our review, and the rest (367 studies)

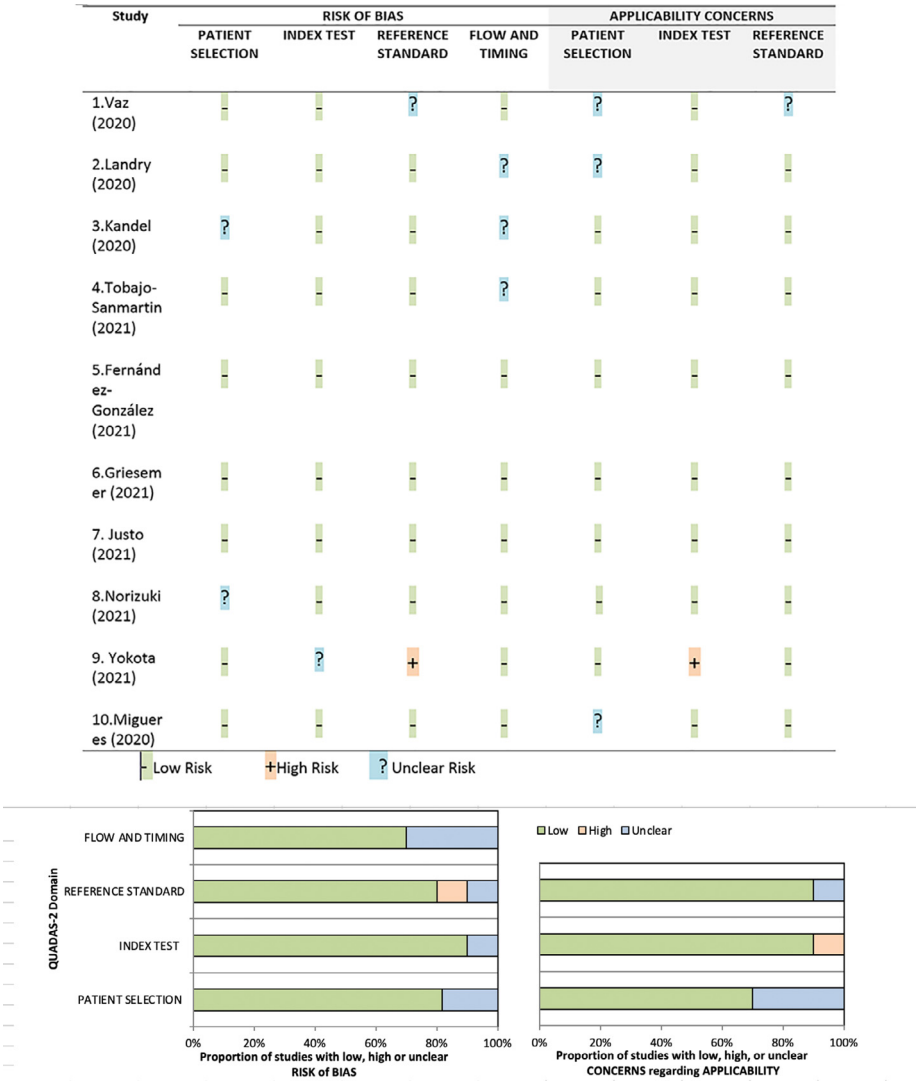

Fig. 2. Assessment of applicability concerns and risk of bias of the included studies.

were excluded. Full texts of the selected 69 clinical studies were reviewed, but only 10 studies met eligibility and were included in the final review (Figure 1). The 10 included studies consisted of 4 "prospective cohorts" and 6 "cross-sectional" studies. These studies were published almost equally in different parts of the world. The mean age of the patients in these papers ranged from 17 to 59 years. For most studies, saliva was self-collected by patients without direct supervision of heath care providers. Patients were advised not to eat or drink before sample collection in a majority of the studies. The sensitivity rate of saliva varied from 85.7% to 98.6% in all studies except in 3; Norizuki et al.[29] and Trobajo-Sanmartín et al.[30] found that the sensitivity of saliva in detecting SARS-CoV-2 might have been lower (63.8% and 51.9%) due to the lower viral load, whereas Fernández-González et al.[31] found a lower sensitivity (66.7%) due to the lack of supervision in collecting saliva samples (Tables I and II).

Assessment of Bias and Methodological Quality

All 10 studies included in our review were assessed for "Applicability" and "Risk of Bias" (Figure 2). Overall, 2 of 10 studies included previously evaluated patients (NPS positives only), enhancing the risk of bias on "Patient Selection" criteria,[29,32] whereas 8 of 10 papers conducted matching sampling, thereby reducing the risk of bias regarding "Patient Selection."[30,31,33-38] All of the studies appropriately reported "reference standard" and "index test" protocols, specifying and referring to the manufacturers related to each RT-PCR test. Yokota et al.[38] implemented RT-qPCR or loop-mediated isothermal amplification (LAMP) in testing NPS samples related to 1 of the cohorts in their study; however, both RT-qPCR and RT-LAMPs were used to assess the saliva samples for both cohorts. This study was scored as high or unclear risk of bias regarding "reference test" and "index test" and on "applicability concerns." To confirm the equivalence of the RT-qPCR and RT-LAMP methods, a scatter plot of time for detecting positive results (Tp) with RT-LAMP against Ct values of RT-qPCR test was presented in the study. Some studies did not provide details on "Timing" and intervals in conducting the tests on collected samples; these studies were rated as unclear risk of bias on "Flow and Timing" criteria.[30,32,35] For most studies, the patient populations matched our criteria; however, 3 studies presented slight concern on "patient selection applicability domain."[33-35]

DISCUSSION

The role of saliva in the screening and detection of SARS-CoV-2 infection has been the focus of many studies in recent months. After reviewing the available SARS-CoV-2 saliva-based literature, we decided to compare the sensitivity of saliva in the detection or diagnosis of SARS-CoV-2 to the NP swab, which has been established as a gold standard test globally.[39] We included only asymptomatic and mildly symptomatic ambulatory patients to have a cohort similar to those seeking professional oral care on a daily basis.

The chance of saliva contamination with other secretions increases if samples are collected from the back of the throat or when collected with forceful coughing or spitting.[23] Therefore, we only included the studies in which saliva was collected passively, without any forceful coughing. We decided to include prospective studies with higher levels of evidence (cohorts and cross-sectionals)[29-38]; all retrospective studies and case reports with a lower level of evidence were excluded. We did not include the letters to editors in our study; however, we took into consideration those letters that

Table I. Main characteristics of the included prospective cohort studies

Study/Author	Location of study	No. of cases	Mean or median age	Saliva collection instructions	Saliva sensitivity
Vaz et al.[32]	Brazil	155	40	Self-collected Asked to spit avoiding mucus or sputum	94.4%
Landry et al.[33]	USA	124	N/A	Asked to not eat or drink for 30 min Advised to let saliva pool in their mouths then spit into sterile container	85.7%
Kandel et al.[34]	Canada	236	42	Instructions given on written form Accumulate saliva in the floor of the mouth for at least 60 seconds and then express saliva into collection container	91%
Trobajo -Sanmartin et al.[30]	Spain	337	17-55	Advised to collect saliva in mouth for a few seconds; then, when saliva is accumulated, to rinse the oral cavity with it and pour the accumulated saliva until an amount of approximately 1 finger has been collected.	51.9% (Ct > 30) 91.6% (Ct < 30)

Ct, cycle threshold.

Table II. Main characteristics of the included cross-sectional studies.

Study/Author	Location of study	No. of cases	Mean or median age	Saliva collection instructions	Saliva sensitivity rate
Fernández-González et al.[31]	Spain	634 (103 children) SC = 208 SVC = 229	36	SVC: Subjects were instructed to produce and pool saliva in their mouths for 1 to 2 min, moving the mouth and passing the tip of the tongue across the cheeks and gums, and then to repeatedly spit a minimum of 1 mL saliva into the collection pot in the presence of a health care worker. SC: Following written instructions "To collect saliva, bow your head forward to allow saliva to pool in the front of your mouth and spit up to a minimum of 1 mL of saliva."	SVC = 86% SC = 66.7%
Griesemer et al.[36]	USA	463	N/A	Patients were instructed to refrain from eating, drinking, chewing gum or tobacco, or smoking for 30 min before collection and to work up saliva in their mouth, not cough, and to drool or gently spit the saliva into the container.	87.1%
Justo et al.[37]	Brazil	76	N/A	Patients were asked to self-collect 2 mL of their saliva in a sterile tube, avoiding mucous secretions from the oropharynx and sputum	98.6%
Norizuki et al.[29]	Japan	20	20-59	Participants instructed not to eat, drink, chew gum, or smoke for 1 h before taking their own saliva samples. Participants instructed how to self-collect saliva samples through video and written instructions including illustrations on arrival at the quarantine facility. Saliva samples self-collected by spitting directly into a sterile tube.	63.8% viral load <10,000 copies/sample 84.7%-100% viral load >10,000 copies/sample
Yokota et al.[38]	Japan	1924	20-50	Saliva samples were self-collected in a sterilized 15 mL polystyrene sputum collection tube.	92%
Migueres et al.[33]	France	123	43	Saliva collected by asking patients to salivate, swill the saliva around their mouth for at least 30 sec, and then spit into a sterile container.	88.2% asymptomatic carriers

SC, self-collection; *SVC*, supervised collection.

contained significant data.[40-48] The other factor that we took into account was the stage of the disease at the time of sample collection (shedding rate of the virus might change throughout the course of the disease); studies entered our review only if the NP and saliva samples were collected at the same time.

Our review revealed that most studies reported a high sensitivity rate for saliva in comparison with the NP (most reports were above 85%). There were only 3 exceptions. The first exception was the study by Trobajo-Sanmartín et al,[30] in which the initial reported sensitivity rate was 51.9%. Although this initial finding was low, it increased to 91.6% when there was a rise in viral load.[30] Another study with a low sensitivity rate was reported by Norizuki et al.[29]; they found the sensitivity rate of 63.8% while the viral load was low (under 10,000 copies/sample). However, the sensitivity rate increased to 84.7% to 100% when the viral load increased to more than 10,000 copies/sample.[29] These data indicate that the staging of the disease can have a significant effect on the sensitivity of the saliva test. Ibrahimi et al.[19] also raised awareness in their systematic review by reporting that the viral load in saliva of presymptomatic patients remains in the range of

detection of the RT-PCR test for several days, both in saliva and nasopharyngeal samples. Ibrahimi et al.[19] also showed that, although sensitivity was slightly lower for saliva samples compared with NP samples, both samples had a value above 80% sensitivity cut-off.

From 50 publications that were included in this study, 1 exclusively analyzed asymptomatic cases, and 8 included both symptomatic and asymptomatic patients. The authors mentioned that it was impossible to separate the data between both populations in the latter group. They also reported they did not observe any differences in concordance of the tests in these studies involving asymptomatic participants.[19] The findings of this study are in agreement with our results; however, we tried to limit our review to asymptomatic and mildly symptomatic cases only, with the goal of minimizing the factors that may affect the accuracy of data. Ibrahim et al.[19] suggested that a formal comparison of NP and saliva samples in asymptomatic individuals would be challenging because it requires screening a large population for a small number of positive cases, and the prevalence is usually low in this group.

In another recent systematic review published by Atieh et al.,[11] the sensitivity of saliva was compared with the NP and oropharyngeal (OP) swabs together. The authors reported that the use of saliva would allow for self-collection of specimens in outpatient and community clinics. These possibilities will help to reduce the overall cost of testing, including health care worker time and PPE requirements, and reduce the health care workers' risk of infection; however, they reported that the ability of the patient to understand the instructions regarding correct sampling and collecting sufficient quantity of saliva could be challenging. This study highlighted that the risk of disease spread may not be eliminated with the use of a saliva sample because the action of "spitting" or "coughing" is required to collect the saliva specimens, and it could provide a route for aerosol transmission.[11] This recommendation is in line with our suggestion to use passive drooling for saliva collection because forceful coughing may increase the chance of contamination and aerosol transmission. Atieh et al.[11] also emphasized the need to identify the sources of SARS-CoV-2 in saliva, such as draining debris from nasopharyngeal epithelium, gingival crevicular fluid, secretions from infected salivary glands, and oral mucosal endothelial cells.

In another systematic review performed by Cañete et al.,[24] 22 publications were included, 17 of which were case series. In this study, the sensitivity of saliva ranged between 20% and 97%, and specificity ranged between 66% and 100%.[24] Our finding was similar to Cañete et al.[24] with regard to the highest range of the sensitivity rate for saliva. However, regarding the lowest sensitivity rate, we found a higher number; this difference might be related to the fact that we only included the cohorts and cross-sectional studies with higher level of evidence. Tsang et al.[22] performed a systematic review on the accuracy of different types of samples in the diagnosis of SARS-CoV-2. They suggested that, in comparison with NP swabs as a gold standard, pooled nasal and throat swabs offered the best diagnostic performance of the alternative sampling approaches for a diagnosis of SARS-CoV-2 infection in ambulatory cases. Saliva and nasal swabs gave comparable and very good diagnostic performance and are clinically acceptable alternative specimen collection methods.[22] Moreira et al.[20] performed a systematic review and meta-analysis regarding the accuracy of saliva in the detection of SARS-CoV-2. They concluded that saliva samples from the oral region provide a high sensitivity and specificity; therefore, these samples appear to be the best candidates for alternative specimens to NPS/OPS in SARS-CoV-2 detection, with suitable protocols for swab-free sample collection to be determined and validated in the future. The distinction between oral and extraoral salivary samples will be crucial because deep-throat saliva (DTS)/posterior oropharyngeal samples may induce a higher rate of false positives.[20]

In the systematic review and meta-analysis by Lee et al.,[26] a slightly lower performance for saliva was shown compared with NP swabs. In this study, papers with nonsynchronous collection of NP and saliva samples were excluded (similar to our study).[26] Another systematic review and meta-analysis by Khiabani et al.[23] showed an overall sensitivity of 97% for bronchoalveolar lavage fluid, 92% for double naso/oropharyngeal swabs, 87% for nasopharyngeal swabs, 83% for saliva, 82% for DTS, and 44% for oropharyngeal swabs among symptomatic patients. Regardless of the type of specimen, the viral load and sensitivity in patients with severe disease were higher than in patients with mild disease and were higher in symptomatic patients than in asymptomatic cases. This study provided evidence for the diagnostic value of different respiratory specimens and supported saliva and DTS as promising diagnostic tools for first-line screening of SARS-CoV-2 infection. Saliva, DTS, and nasopharyngeal swab showed approximately similar results, and sensitivity was directly related to the disease severity. They disclosed that none of the specimens had appropriate diagnostic sensitivity for asymptomatic patients.[23] This last finding is in contrast with our results, which showed a high sensitivity rate in using saliva specimens in asymptomatic patients. Another review by Sagredo-Olivares et al.[25] reported that RT-qPCR was the most widely used test to diagnose SARS-CoV-2 in saliva. This test demonstrated a

sensitivity of 84.2% and a specificity of 98.9% compared with the nasopharyngeal swab RT-qPCR results. In this review, the importance of detecting asymptomatic people to control the spread of the pandemic and find a diagnostic method with high sensitivity and specificity were highlighted.[25]

Another area reviewed in our study was the regions related to each published article, and we found the publications to be equally representative of different regions worldwide. This finding is different from the findings of Sagredo-Olivares et al.[25] They showed that countries with a higher number of cases and a high level of scientific ability, such as the United States, Japan, and China, have a higher rate of publications. Another limitation reported in the study by Sagredo-Olivares et al.[25] was the fact that samples were collected by patients, who did not specify whether they were instructed in detail on how to perform the procedure, so it is not known if these samples were taken correctly or if the amount collected was sufficient to perform the analysis.[25] In our study, we reviewed the details of instructions regarding sample collection. We did not find any difference in sensitivity results when comparing supervised vs self-collected saliva samples, except in the study by Fernández-González et al.,[31] in which supervised collected saliva samples showed a higher level of sensitivity compared with self-collected saliva samples (86% vs 66.7%).[31]

In a few letters to editors, the authors compared the sensitivity of saliva with NPS through their prospective studies. For example, Williams et al.[41] and Skolimowska et al.[42] reported a diagnostic value for saliva to detect SARS-CoV-2 and explained that the viral load was much higher in NPS samples compared with saliva samples. Most of the studies included in our review found a higher level of viral load and lower cycle threshold (Ct) value for NPS in comparison with saliva. This difference was reported as significant in some of these studies[30,31,35,36] and not significant in a few others.[32] The study by Yokota et al.[38] reported the viral loads to be equivalent between NPS and saliva samples in asymptomatic individuals. Williams et al.[41] also emphasized the fact that there is a correlation between Ct value and days from symptom onset. This finding was in line with a study by Justo et al.,[37] which reported NPS had lower Ct value in all days after symptom onset compared with saliva, and a significant difference was only seen on days 1 to 4. Justo et al.[37] also found the highest Ct value for both saliva and NPS during the days 7 to 9. A letter to the editor by Caulley et al.[45] also revealed that standard diagnostic methods of nasopharyngeal and oropharyngeal swabs detected more COVID-19 cases than saliva testing among patients who were asymptomatic but at high risk or who were mildly symptomatic. Another letter to the editor by Wyllie et al.[40] indicated a greater variation in human RNase P (Ct) values in NPS specimens compared with saliva specimens collected from a cohort of asymptomatic health care workers. This level of variation may be contributing to more numbers of false negative cases in NPS compared with saliva.[40]

Although the role of saliva in the detection of COVID-19 has been the focus of multiple publications in recent months, the heterogeneity in methods for saliva collection, assays used for virus detection, diverse age, sex, ethnicity, and the severity and stage of the disease may have affected the reported sensitivity of saliva compared with NPS. Some of these limitations have been referred to in a review by Tan et al.,[39] which suggested that the standardization of salivary testing methods is necessary to improve detection rates and resolve discrepancies between studies. Our review revealed similar limitations. The majority of the studies had not discussed in detail the nature of the disease or the stage of the disease when samples were collected.[39] Most studies specified that the samples were collected from asymptomatic/mildly symptomatic patients; however, it was not reported if these patients were asymptomatic carriers or in a presymptomatic phase (or early stage) of the disease (except in the study by Norizuki et al.,[29] in which the stage of the disease was explained upon enrollment). Another limitation was the absence of a detailed explanation regarding the accuracy of sample collection; few studies reported in detail regarding the level of instructions to the patients and if patients were supervised while collecting saliva (Tables I and II). These limitations need to be addressed in future studies.

CONCLUSION

While including only prospective studies with a high level of evidence (cohorts and cross-sectional studies), our review showed that passively collected saliva (when collected without forceful coughing) has a high sensitivity rate to detect SARS-CoV-2 in asymptomatic and mildly symptomatic ambulatory patients compared with NP swabs. The way instructions were given to the patients to collect saliva had no effect on the study results for most studies (except one).

Our study revealed limited available information on the true value of saliva in the diagnosis and or detection of SARS-CoV-2 in ambulatory patients. Future investigations should be inclusive of stages of the disease, detailed methodology for collection and assessment of saliva, and specific instruction at the time of sample collection.

DISCLOSURES

None.

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