THE EFFECTIVENESS OF SALIVA BASED TEST IN THE DETECTION OF COVID-19 AMONG SUSPECTED PATIENTS. A LITERATURE REVIEW

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ABSTRACT

Background: The World Health Organization declared a pandemic when severe acute respiratory syndrome coronavirus (SARS-CoV)-2 spread globally. Fever, cough, weariness, minor dyspnea, sore throat, headache, conjunctivitis, and gastrointestinal difficulties are the primary COVID-19 symptoms. Saliva droplets and nasal discharge may spread this extremely contagious sickness. Real-time PCR diagnoses nasal swab, tracheal aspirate, and broncho-alveolar lavage samples.

Objective: To evaluate the effectiveness of saliva based test in the detection of covid-19 among suspected patients.

Material & Methods: This review study followed PRISMA guidelines for honest reporting of systematic reviews and meta-analyses. MEDLINE (PubMed), Scopus, CENTRAL, Science Direct, Web of Science, and Google scholar were searched till December 2020. Only SARS-CoV-2 clinical features and therapy papers were eligible. This review excludes non-scientific views, reports, letters, and news stories. This review asked: Is saliva a better SARS-CoV-2 diagnostic specimen than RT-PCR pharyngeal swab tests? Original, full-text English papers on saliva as a COVID-19 diagnostic specimen were eligible for review. Excluded were letters, narrative reviews, animal studies, and duplicates. Searches were not limited by publication date. Thus, all relevant evidence up to December 2020 that satisfied inclusion criteria was examined.

Results: Saliva is an excellent specimen for community and population-based screening due to its strong diagnostic accuracy and ease of using material without transport medium for SARS-CoV-2 RT-PCR. self-generated saliva sample without coughing. This non-invasive saliva collection method may minimize aerosols and infection risk for clinic staff. Although saliva samples may be combined with sputum, evaluating them may be easier than bronchoalveolar lavage fluid for those with severe illness.

Key words: SARS-CoV-2,RT-PCR, Oropharyngeal and nasopharyngeal swabs.

INTRODUCTION

The World Health Organization has declared a pandemic due to the widespread transmission of the severe acute respiratory syndrome coronavirus (SARS-CoV)-2, a new coronavirus belonging to the similar group as SARS-CoV and Middle East respiratory disease coronavirus.[1] Temperature, coughing, weariness, mild breathlessness, scratchy throat, headache, conjunctivitis, and digestive problems are the predominant signs and manifestations of COVID-19. Employing specimens from a nose swabs, tracheal aspirate, or broncho-alveolar lavage, real-time PCR is employed as a testing technique. There is currently no proof that COVID-19 can be treated effectively.[1]

Stopping the coronavirus disease 2019 (COVID19) pandemic requires the quick and precise diagnosis of the SARS-CoV-2 coronavirus in patient samples. There are currently little studies assessing the sensitivity of various sample categories for the recognition of SARS-CoV-2. The recommended sampling route for SARS-CoV-2 testing in Canada is nasopharyngeal (NP) swabs; early findings indicate that NP swabs may be more sensitive than oropharyngeal swabs for SARS-CoV-2 diagnosis.[2,3,4] This condition's rapid

spreading is due to the fact that it is very contagious, and it is thought to spread by nasal secretion and saliva particles. In light of the present emergent scenario, developing precise and quick diagnostic checking procedures for SARSCoV-2 is crucial for containing the epidemic in the general public and in medical facilities. The greatest reliable technique for diagnosing suspicious individuals at the time this publication was written was PCR-based nucleic acid detection.[5] Oropharyngeal and nasopharyngeal swabs are the suggested upper respiratory tract specimen options for SARS-CoV-2 diagnostic testing since viral pneumonias often do not produce purulent sputum. The intimate interaction between medical staff and sufferers necessary for the gathering of these specimen types raises the biosafety threat to staff members by generating aerosol particles. Additionally, patients may experience some pain while having oropharyngeal or nasopharyngeal swabs used to gather samples. These techniques may potentially result in hemorrhaging in the desired tissue, particularly in those with thrombocytopenia.[5] Oropharyngeal and NP swab retrieval, meanwhile, may be painful for sufferers and dangerous for medical personnel. Additionally, accessibility to different swab types has been restricted as a consequence of current global supply-chain bottlenecks. Due to its involvement in the COVID-19 pandemic's viral transmission, saliva is one of our worst enemies. But it may also be our ally since it might provide a non-invasive alternative to the invasive nasal swabs now used in illness diagnosis. Fast and precise screening of questionable patients is one of the primary issues with epidemic prevention and controlling of any infectious illness. Apart from the sensitivity and specificity of laboratory procedures, choosing the right locations for sample collection is crucial. The tissue affinity of the intended virus, the technique's cost-effectiveness, and the sufferers'

and doctors' wellbeing should all be taken into consideration while choosing the best sample strategy.[6] Furthermore, the goal of this review research is to compile the most recent data on the validity of saliva as a diagnostic sample in COVID-19 patients.

MATERIAL AND METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for clear documenting of systematic reviews and meta-analyses were used to perform this review. Science Direct, Web of Science, MEDLINE (PubMed), Scopus, The Cochrane Central Register of Controlled Trials (CENTRAL), Google Scholar, and Science Direct were all thoroughly searched until December 2020. Only articles discussing the clinical traits and therapies for SARS-CoV-2 qualified for inclusion. This evaluation did not include any non-scientific views, reports, letters, or news stories. Is saliva a valid diagnostic material for SARS-CoV-2 probable individuals when contrasted to or pharyngeal swab tests based on RT-PCR methodology? was the review's main research topic. The inclusion of original, English-language full-text papers assessing saliva as a diagnostic specimen for identifying COVID-19 patients was one of the inclusion requirements for research chosen for evaluation. Animal studies, narrative reviews, letters, and duplicated papers were all disqualified. The publishing date was not a limitation on the search technique. As a result, all pertinent data up to December 2020 that satisfied the eligibility criterion was evaluated.

RESULTS

Michailidou E et al[7] reported after conducting a comprehensive overview of saliva as a specimen for the detection of SARS-CoV-2, after utilizing the very recent methods for the salivary diagnostics i.e. the molecular test , that the virus must be isolated in cell cultures and its genome sequences must be fully analyzed and the viral nucleic acids are detected. They discovered that none of the viruses currently in existence make utilization of saliva as an appropriate specimen for the detection of viral RNA, antigens, and antibodies. They revealed that the already documented analysis lacks a sufficient quantity of publications, significant patient cohorts, and prescriptive patient participation and exemption requirements. They also reported that it is urgently necessary to continue working in the profession and to assess how well the research is performing.

To demonstrate saliva's emergence as a viable substitute for nasopharyngeal/ oropharyngeal swabs for COVID-19 diagnosis and observation of it transmissibility in the population, Sapkota D et al[8] performed the research in August 2020. The drawbacks of using nasopharyngeal/oropharyngeal swabs are greatly avoided by saliva gathering, which is a non-invasive method with the option of self-collection. Nonetheless, they came to the conclusion and made the suggestion that saliva-based screening could be a substitute to the more frequent nasopharyngeal / oropharyngeal swabs for diagnosing and tracking COVID-19.

The usage of saliva-based SARS-CoV-2 screening has a number of therapeutic benefits and is supported by science. The reciprocal interaction between COVID-19 and saliva will, therefore, need to be better understood in order to adopt less intrusive diagnostic procedures and enable the widespread use of genetic testing, a critical component of an

epidemic prevention plan. Finding salivary biomarkers connected to COVID-19's onset and development may help distinguish between silent, mild, moderate, and severe illness. The creation of point-of-care devices, which may be very helpful for studying the evolution of infectious diseases and immune reactions in community research, may be facilitated by information of this sort.

The investigation was carried out by Fernandes LL et al[9] to examine the literature that demonstrates the value of saliva as a biofluid in the identification and surveillance of COVID-19. According to their plan, on July 22, 2020, they performed their approach using the grey literature as well as five electronic sources (PubMed, Embase, LILACS, Scopus, and Web of Science) (hand search in the reference lists). MeSH terms were selected as the general controlled vocabulary and keywords, while language, year, and publishing category restrictions were not applied to the analyses. They came to the conclusion that SARS-CoV-2 could be reliably detected in individuals with COVID-19 and that its diagnostic efficiency was on par with existing norms (nasopharyngeal and throat swabs). The knowledge of salivary biomolecules that may be exploited for salivary diagnostics in the setting of COVID-19 infection, though, is lacking. Additionally, investigations with broader cohorts at various phases of COVID-19 infection are required to demonstrate the efficacy of saliva in COVID-19 diagnosis. Salivary specimens enable for additional diagnostic techniques, such as the examination of bioanalytes that may be utilised in quick diagnostic tools in addition to the direct recognition of the pathogen. This assessment should serve as a roadmap for global initiatives to develop quick COVID-19 detection and surveillance methods using saliva.

The research was carried out by Ceron JJ et al[10] to emphasize newly available data and prospective views on the usage of saliva as a specimen for laboratory testing of the Covid-19. Saliva may potentially be used in the setting of Covid-19 by directly detecting

the virus, quantifying the specific immunoglobulins generated towards it, and assessing the patient's non-specific innate immune reaction, according to their findings and recommendations. A fuller understanding of possible alterations in the saliva proteome may also make it possible to find novel diagnostic biomarkers or provide light on the condition's underlying causes. Saliva may give important clinical information about the condition and may eventually be incorporated in specimen gathering recommendations for the diagnosis, treatment, and control of Covid-19 with the establishment of acceptable sample gathering and processing procedures and the deployment of sufficient tests.

In July 2020, a research was undertaken by Hamid H, et al[11] to ascertain the function of human saliva as a screening biofluid in point-of-care technology. They discuss the unique coronavirus disease 2019 (COVID-19) pandemic, which has been labelled as a manageable pandemic and has brought about a complete halt to efforts throughout the globe to contain the epidemic using health systems. Medical care professionals are battling day and night all across the world. Nowadays, bronchoalveolar lavage, sputum, urine, blood, and nasopharyngeal and oropharyngeal swabs are used in fast screening. They did note, though, that substantial viral loads of SARS-CoV-2 RNA are being discovered in salivary gland and saliva, perhaps highlighting the significance of this biofluid for evaluating the illness in asymptomatic state, as shown by research discussed in this article. The creation of a mass screening tool employing saliva POC technology is crucial given the pandemic's astonishingly high transmission rate at the moment. POC technique, which uses saliva as a liquid biopsy to immediately diagnose COVID-19 patients, may mark a significant turning point in the field of quick identification. In the

interests of controlling and reducing the illness, this would significantly aid in identifying and isolating possible transmitters and contacts.

The investigation was carried out by Kapoor P et al[12] to investigate the data supporting the use of saliva as a different testing specimen in SARS-CoV2 conditions. They carried out a scoping assessment of the literature to investigate the usefulness of saliva samples for COVID-19 diagnosis. In June 2020, a comprehensive review of the literature was carried out using three databases: Pubmed (P), Web of Science (WOS), and Scopus, as well as specialised COVID issues of PubMed, WHO, and International Association of Dental Research COVID Resource, hand search (HS), and reference tracking. Despite the fact that they came to the conclusion that significant SARS-CoV-2 viral loads in saliva (>5 log10 average) were seen within the first week following the start of symptoms in studies examining viral load in paired NPS/saliva samples or serial saliva samples. Research comparing patients with moderate illness to those with serious condition have shown that individuals with severe disease had considerably longer median viral durations (2–3 weeks) and higher viral loads. Saliva may be used as a valid supplemental material in the first screening of SARS CoV-2 in a population or inpatient setting, according to the study's ultimate judgment.

Vinayachandran D et al[13] undertook the research to explore the new Coronavirus 19, to describe the potential function of saliva/salivary glands, and gingival crevicular fluid. We also discuss further methods that such investigations may be initiated. However, it was ultimately concluded that more research is necessary to fully understand the usefulness of saliva as a rapid, non - invasive diagnostic method and the numerous opportunities it offers for exploration during the duration of the disease phase, prognosis, or existence of

any antibodies to the novel COVID-19 virus. Customized pharmacological therapy may also be made possible by the participation of any additional receptors or cellular proteases that may provide further information on the biology of the epidemic sickness.

The first study on the uniformity and dependability of SARSCoV-2 viral RNA detection in saliva samples was carried out by Czumbel LM et al[14]. They looked for papers that fit the criteria that were released between 1 January and 25 April 2020 in the Cochrane Library, Embase, Pubmed, Scopus, Web of Science, and clinical trial databases. Raw statistics were gathered on the overall number of tests done as well as the amount of positive results. By using the Freeman-Tukey transformation and score confidence interval estimation, the percentage of positive tests in the aggregated dataset was obtained. They concluded by noting that saliva tests provide a viable alternative to nasopharyngeal swabs in the diagnosis of COVID-19. Further self collection of samples for COVID-19 testing may be possible with optimised and verified saliva tests. Regarding the specificity and sensitivity of tests based on saliva, there are still a lot of unanswered concerns. Therefore, much more study is required before regularly introducing SARS-CoV-2 testing utilising saliva samples in clinical practise.

The research was carried out by Williams E et al. There may be potential for SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) testing in distant and low-resource settings in August 2020 and they employed the saliva as a diagnostic sample. The capability to identify SARS-CoV-2 in saliva over a one-week period, according to them, is a significant result that opens up new possibilities for saliva testing as an early diagnostic test in difficult-to-reach communities where there may be few alternatives. The reliability of SARS-CoV-2 RNA detecting in salivary specimens throughout this

time period in tropical climes with greater room temperature and moisture, as well as with RT-PCR objectives employing different sections of the SARS-CoV-2 genome, need to be evaluated in other research.

When they believe there is a necessity for a speedy and simple way to acquire a non-invasive specimen for the tracking of this novel coronavirus, Pasomsub E et al16 completed the cross-sectional research in November 2020 to explore the possible utilisation of saliva samples as a non-invasive tool for the diagnosis of COVID-19 (severe acute respiratory syndrome coronavirus 2; SARS-CoV-2). During the COVID-19 outbreak, they prospectively collected saliva samples and a standard nasopharyngeal and throat swab from patients visiting an acute respiratory infection clinic in a university hospital. The two samples were subjected to real-time polymerase chain reaction (RT-PCR), and the outcomes were evaluated. They obtained 200 sets of specimens for their investigation. The mean (interquartile) age of the 69 participants (34.5% of whom were male) was 36 (28 to 48). The proportion of COVID-19 as determined by nasopharyngeal and throat swab RT-PCR was 9.5% when used as the benchmark criterion. The saliva sample RT-PCR had a sensitivity and specificity of 84.2% (95% CI 60.4%e96.6) and 98.9% (95% CI 96.1%e99.9%), respectively. A comparison of the two samples' concordance revealed a 97.5% perceived concordance. Eventually, they came to the conclusion that saliva may serve as a substitute specimen in the COVID-19 diagnostic. Both the gathering and the production of aerosols are non-intrusive. Given the convenience of specimen collection and effective diagnostic capabilities, this technology may make illness diagnosis easier.

Country	Study year	Sample size	Study design	Study findings
Greece	2020	Not mentioned	Review article	Saliva collection is a non-invasive procedure that causes the patient no pain and enables the patient to use home self-sampling methods to safeguard medical professionals from exposure to the virus.
China	2021	Not mentioned	Review article	For COVID-19 diagnosis and disease monitoring, saliva-based screening may be a substitute to the more popular nasopharyngeal swabs
Brazil	2020	28 studies	Systematic search	Saliva's potential for detecting COVID-19 infection is still being investigated.
Spain	2020	Not mentioned	Research report	Saliva may provide helpful clinical data regarding the condition.
Saudi Arabia	2020	Not mentioned	Review article	Salivary glands and saliva have substantial viral loads of SARS-CoV-2 RNA.
India	2021	17 studies	Scoping review	In a community or hospital setting, saliva may be used as a useful supplemental specimen for the first testing of SARS CoV-2.
UK	2020	42 patients	Not mentioned	The virus that the creation of a mass screening method for COVID19 patient diagnosis is effectively accomplished using saliva
India	2020	Not mentioned	Prospective study	The advantages of using saliva as a rapid, non-invasive diagnostic tool and the range of options
	2020	96 records	meta-analysis	A possible substitute for NPS in the diagnosis of COVID-19 is saliva testing.
Australia	2021	Not mentioned	*in vitro* study	It's significant because SARS-CoV-2 may be found in saliva for a whole week.

DISCUSSION

According to this review's observations, saliva has a strong diagnostic reliability and the ability to be used as a sample without transport medium for SARS-CoV-2 RT-PCR. In population-based screening and community environments, saliva is a possible specimen of choice. According to current research, SARS-CoV-2 was found in posterior oropharyngeal saliva samples, and the virus was particularly active when the sickness first manifested.[18,19] According to their methodology, a saliva specimen was taken in the earliest morning after the patient cleared their throat and coughed. In our research, the participant self-generated a saliva specimen without having to cough up. Saliva gathering with this non-invasive method may produce less aerosols and lower the risk of infection for clinic staff members. While it is possible that the samples were mingled with sputum and saliva, the likelihood of a person coughing up phlegm is quite low, since a recent research revealed that a dry cough was the most prevalent complaint in around 80% of patients at the beginning of the disease.[20] A comparability of diagnostic investigations between saliva sample and confirmed-case bronchoalveolar lavage fluid or convalescence serum titre has not been made, despite the possibility that examining saliva samples would be advantageous as a quick technique. In a current investigation, the virus was found at several places, and the nasal swab had a lower test positive rate (63%) than bronchoalveolar lavage fluid (93%).[21] Hence, for those with serious illness, a lesser incidence of SARS-CoV-2 recognition from saliva than from bronchoalveolar lavage fluid may be feasible. Intriguingly, nasopharyngeal and throat swabs from two specimens did not reveal any SARS-CoV-2 detection. The ORF1ab and N genes' Ct values for these two samples were, correspondingly, 33.9 and 34.8 in one specimen and 36.2 and 33.7 in

another. Eventually, these two people claimed to have anosmia. Thus, the outcomes of these tests could reflect an actual illness. It is necessary to do further research on the salivary specimen's output as a supplemental diagnostic test for COVID-19. The research offers a number of advantages.

In order to reduce the possibility of a spectrum influence, we prospectively gathered data on patients who were consistently at high risk of COVID-19, including those with acute respiratory symptoms and warning indicators. Additionally, the reference benchmark was used to confirm all patients who had been enrolled. The scope of the condition extends from asymptomatic, through upper respiratory tract symptoms and pneumonia, to acute respiratory distress syndrome, although our research primarily concentrated on saliva screening among those under examination who were unwell.[22,23] As a result, it is uncertain how well the saliva test performs in detecting SARS-CoV-2 in asymptomatic people. The decrease of COVID-19 instances in Bangkok since April 2020 also placed a limit on the number of cases included in our analysis. Quick and precise assessment of questionable individuals is one of the primary issues with pandemic prevention and control of any infectious illness. Apart from the sensitivity and specificity of laboratory procedures, selecting the right locations for sample collection is crucial. The tissue affinity of the intended virus, the technique's cost-effectiveness, and the sufferers' and doctors' wellbeing should all be taken into consideration while choosing the best sample strategy.[23] In this research, we ranked the available data on saliva's validity as a diagnostic test in COVID-19 patients. According to the majority of the research included in this review, there is no statistically meaningful variation in viral load between nasopharyngeal or sputum specimens and salivary specimens. These investigations

recommended using saliva as a non-invasive specimen type for the detection of SARSCoV-2 and for tracking its viral burden.[24-27] In earlier research, saliva and nasopharyngeal aspirate samples analysed using an automated multiplex molecular assay recognised for point-of-care testing showed a high degree of comprehensive concordance.[28,29] According to these research, the technique used to obtain saliva and the kind of collection equipment used are crucial factors in the use of saliva as a diagnostic specimen. Human saliva may be divided into three primary categories: entire saliva, parotid gland, and minor gland. Each category has a different technique of collecting.[28] Collecting the whole saliva of the suspicious individuals is beneficial when the sampling's goal is to apply molecular tests to identify respiratory viruses.[26] The sufferers should be told to expectorate saliva into a sterile container in this case. Saliva should be between 0.5 and 1 ml in volume. Viral transport medium (VTM) in the amount of 2 ml should then be poured to the container. The subsequent procedures will be carried out in accordance with guidelines for the relevant RT-PCR technology at the microbiology lab. The different approaches to collecting the specimens may account for the poor concordance rate of saliva with nasopharyngeal specimens seen in Chen et al study.[24]

The detection rate of SARS-CoV-2 in pure saliva fluid released from the opening of salivary gland canals was reported in this investigation. In contrast, participants in other research were instructed to spit out saliva into sterile containers, therefore the saliva samples in those investigations mostly consisted of sputum from the lower respiratory tract. Therefore, the directions should adequately describe the proper process to the people in order to increase the sensitivity of salivary testing in the approach of identifying the suspected COVID-19 patients. In clinical practise, using saliva samples for SARS-

CoV2 diagnosis offers various benefits. First off, collecting saliva is a non-invasive process that spares patients from pain, as opposed to using nose or throat swabs. The ability to collect samples outside of hospitals is the second benefit of utilising saliva as a specimen. The suspicious individuals may give this sample approach on their own without the assistance of medical staff. As a result, this approach may reduce the possibility of nosocomial SARS-CoV-2 transmission. Additionally, since qualified healthcare professionals are not required for the collection of saliva samples, the wait time for suspected patients will be shorter. This is essential in crowded clinical environments when a lot of people need screening. Saliva taken from COVID-19 patients may contain live viruses that may spread from one person to another, according to the findings of a study that was included. These findings confirm the need for barrier-protection gear to be used as a preventative precaution by all healthcare professionals working in clinic and hospital settings during the COVID-19 pandemic. It should be noted that this research has a number of shortcomings. First off, there is a dearth of information accessible due to the recent start of the SARSCoV-2 epidemic and discovery. Second, the included studies in this analysis did not assess other variables like illness severity or disease progression that may have an influence on the viral detection rate. Last but not least, as all of the chosen studies only involved verified COVID-19 patients who were hospitalised, more research need to be done in outpatient settings.

CONCLUSION

Saliva may serve as a substitute specimen for the diagnosis of COVID-19, according to this study. Both the collection and the production of aerosols are non-intrusive. Given the

convenience of specimen collection and effective diagnostic capabilities, this technology may make illness diagnosis easier.

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