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Saliva as a diagnostic sample of SARS-CoV-2: an integrative review

Saliva como método diagnóstico do SARS-CoV-2: uma revisão integrativa

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ABSTRACT

In March 2020, the disease caused by the new coronavirus (SARS-CoV-2) was characterized as a pandemic. Due to the magnitude that the disease has reached and its unprecedented character, a growing scientific interest in the disease has emerged, with searches to find new diagnostic methods, increasing the speed to obtain test results and, consequently, a better epidemiological mapping of the disease. This integrative review aims to analyze the main scientific evidence on the use of saliva as a diagnostic method for COVID-19. In the present integrative review, searches were conducted in four electronic databases in March 2022, namely: PubMed, in which results were included exclusively in English, and in the platforms Google Scholar, SciELo and Virtual Health Library (VHL), with the inclusion of results strictly in Portuguese. Different keywords were used according to the dominant language of the databases, being in PubMed in English language chosen "SARS-CoV-2", "saliva", "diagnosis", "viral load" and "coronavirus COVID-19" and in the other platforms, in Portuguese language "saliva", "covid" and "diagnosis". Among the 45 articles included and analyzed, more than half classified saliva as an alternative or complementary diagnostic method. Yet, only three articles out of the total number classified saliva as an unviable sample for diagnostic testing. Thus, saliva showed positive results as a diagnostic option and for COVID-19 follow-up and monitoring. However, despite the limitations of the studies, the saliva sample in pediatric patients suggests having low sensitivity.

Keywords: COVID-19. COVID-19 Tests. Saliva. SARS-CoV-2.

RESUMO

Em março de 2020, a doença causada pelo novo coronavírus (SARS-CoV-2) foi caracterizada como uma pandemia. Em decorrência da magnitude que a doença alcançou e seu caráter inédito, um crescente interesse científico sobre a mesma surgiu, com buscas para se encontrarem novos métodos diagnósticos, aumentando a velocidade para a obtenção dos resultados dos testes e, consequentemente, um melhor mapeamento epidemiológico da doença. Esta revisão integrativa tem como objetivo analisar as principais evidências científicas sobre a utilização da saliva como método diagnóstico da Covid-19. Na presente revisão integrativa, foram realizadas buscas em quatro bases de dados eletrônicas, em março de 2022, sendo elas: PubMed, em que foram inclusos resultados exclusivamente em inglês, e nas plataformas Google acadêmico, SciELo e Biblioteca Virtual de Saúde (BVS), havendo a inclusão dos resultados restritamente em português. Foram utilizadas diferentes palavras-chave de acordo com a linguagem dominante das bases de dados, sendo no PubMed em língua inglesa escolhidos ‘’SARS-CoV-2´´, ‘’saliva’’, ‘’diagnosis’’, ‘’viral load’’ e ‘’coronavirus Covid-19’’ e nas demais plataformas, em língua portuguesa ‘’ saliva’’, ‘’ covid’’ e ‘’ diagnósticos’’. Dentre os 45 artigos incluídos e analisados, mais da metade classificaram a saliva como um método diagnóstico alternativo ou complementar. Ainda, apenas três artigos do número total classificaram a saliva como uma amostra inviável para os testes de diagnóstico. Dessa forma, a saliva mostrou resultados positivos como uma opção de diagnóstico e para o acompanhamento e monitoramento da Covid-19. No entanto, apesar das limitações dos estudos, a amostra salivar em pacientes pediátricos sugere ter baixa sensibilidade.

Palavras-chave: Covid-19. Saliva. SARS-CoV-2. Testes para Covid-19.

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INTRODUCTION

In March 2020, the World Health Organization (WHO) characterized the disease caused by the new coronavirus as a pandemic, due to the increase of newly infected cases and a large number of deaths in a short period. About COVID-19, it is known that the infected patient can be asymptomatic, however, when symptomatic, some of its symptoms are characterized by fever, cough, coryza, sore throat, and, in more severe cases, have breathing difficulties (Xu et al., 2020; Yan et al., 2020; Zhong et al., 2020; Huang et al., 2021; Matuck et al., 2021). SARS-CoV-2 has an affinity for ACE-2 (Angiotensin-converting enzyme 2), which is expressed throughout the respiratory tract, kidney, and myocardial cells, for example, as well as in the tongue papillae, salivary glands, and oral mucous membranes. Given this interaction and the large expression and distribution of ACE-2 in the oral cavity, a high potential for transmission and the presence of the virus in saliva is suggested (Hung et al., 2020; Yan et al., 2020; Huang et al., 2021; Lee, Herigon, Benedetti, Pollock & Denkinger, 2021).

Thus, the timely and accurate detection of the virus has led many diagnostic methods to be used, such as blood, stool, urine, sputum samples, bronchoalveolar lavage, nasopharyngeal and posterior pharyngeal swabs, and also salivary samples (Matuck et al., 2021). The latter has shown great results for viral detection, since it has a significant amount of oral mucosal samples, and consequently an uptake of the ACE-2 receptors, making COVID-19 diagnosis more accurate (Hung et al., 2020).

Because of this potentiality, saliva is fluid in the oral cavity, produced by the salivary glands, and is seen as a good option for the diagnosis of SARS-CoV-2, where the patient easily expels the sample. Because it is collected without the help of healthcare professionals, there is a lower chance of contagion of the disease compared tothe nasopharyngeal and posterior pharyngeal swab sampling methods. In the latter, the collections are made by trained professionals and also generate more significant discomfort for patients, especially in the nasopharyngeal area, with greater sensitivity of the respiratorymucous membranes, which may induce sneezing, coughing, and even cause trauma to them (Yan et al., 2020).

Therefore, because COVID-19 has multiple presentations of clinical symptoms, it is imperative to have optimal methods for diagnosing and monitoring cases infected with it. Thus, this integrative review aims to evaluate the potential of saliva as a diagnostic method for COVID-19 and its role in COVID-19 control and monitoring.

MATERIAL AND METHODS

The integrative review was characterized by searching for scientific articles in four electronic databases, namely: PubMed, Google Scholar, SciELO, and Virtual Health Library. In all these databases there was no specification as to the year of publication. The articles that contemplated cohort study, case series, case study, transversal study, comparative and randomized clinical trials were included in this review.

As keywords and choice of languages to be included in each search, below are the specifics of each platform; furthermore, in all databases the Boolean operator "AND" or "and", depending on the searched platform, were used to associate the keywords.

a) PubMed: the keywords " SARS-CoV-2", " saliva", "diagnosis", "viral load" and "coronavirus COVID-19" were used from which results written in the English language were included.

b) Google Scholar, SciELO, and Virtual Health Library (VHL): the results were restricted to the Portuguese language, using the keywords "saliva", "covid" and "diagnóstico".

The search was scheduled to be performed in a single day by only one researcher responsible for its execution (BPN). First, the titles were read and evaluated for compliance with the pre-established criteria. Later, those included had their abstracts read to observe the research theme.

Those that remained had their abstracts read in full. When there were doubts in the reading of the abstracts or the articles in full, a second researcher (BFO) was called to discuss and make a decision about the permanence of the article in the final review, as well as to interpret the results of the articles.

Also, regarding the type of articles, letters to the editor, *preprints,* literature reviews and systematic and integrative reviews were excluded. Those articles that were not in the established language, duplicated, or off-topic, for example, the use of saliva for the diagnosis of viruses other than SARS-CoV-2, were excluded.

RESULTS AND DISCUSSION

After conducting the search in March 2022, reading the titles and abstracts, and applying the inclusion and exclusion criteria, 45 articles were selected, of which 36 were included in PubMed, two in the Virtual Health Library (VHL), two in SciELO, and five in Google Scholar (Figure 1). The articles analyzed in this review were studies based on the efficacy of salivary samples as a diagnostic method for COVID-19 and their comparison with other diagnostic methods. The studies presented correlated the viral load by the period in which these tests were followed up.

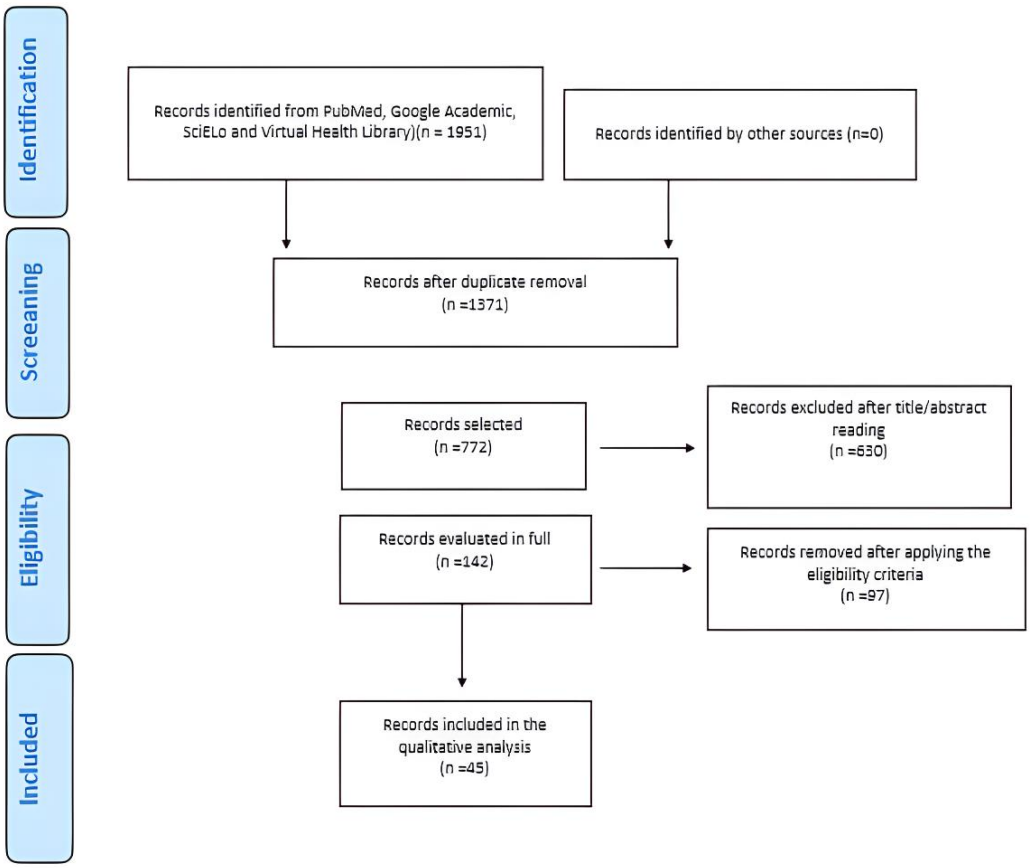

Figure 1. Flowchart of the integrative review search.
Source: The authors.

Of all the articles selected, 14 stated that saliva is an excellent diagnostic method in the initial period of the disease since the tests showed a higher viral load in this fluid in the first week after the onset of symptoms. On the other hand, 3 of 45 articles considered saliva as ineffective for diagnosis due to "false negatives", which occurred frequently after the first week of virus infection.

As can be seen in Table 1, one study carried out with children diagnosed with COVID-19 found saliva samples to have a lower viral load rate when compared to nasopharyngeal samples (Kam et al., 2020). In addition, 27 articles showed saliva only as an alternative method for patients who have contraindications to nasopharyngeal collections or in places where health professionals cannot act directly, since the patients themselves can collect their salivary samples.

Table 1
Articles found in the review that analyzed saliva as a diagnostic sample for COVID-19.

Scientific Evidence	First author/Year	Geographic Region	Article Title	Evaluated Parameters	Conclusions
Cohort study	To et al. (2020)	The University of Hong Kong, Pokfulam, Hong Kong Special, Administrative Region, China.	Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study	1. Time 2. Viral load 3. Different methods	Effective method.
Cohort study	Hung et al. (2020)	The University of Hong Kong, Pokfulam, Hong Kong Special Administrative Region,China.	Early-morning vs spot posterior oropharyngeal salivafor diagnosis of SARS-CoV-2 infection: implication of timing of specimen collection for community-wide screening	1. Time 2. Viral load	Effective method.
Case Series	Yoon et al. (2020)	University Guro Hospital, Korea University, College of Medicine, Korea.	Clinical significance of a high SARS-CoV-2 viral load in the saliva	1.Time 2.Viral load	An alternative method (first days after symptoms).
Case Study	To et al. (2020)	The University of Hong Kong, Hong Kong Special Administrative Region, China.	Consistent detection of 2019 novel Coronavirus in saliva	1. Time 2. Viral Load	An alternative method (in cases wherecollection of samples from the nasopharyngeal area is contraindicated).
Cohort study	Kam et al. (2020)	National University ofSingapore, Singapore.	Clinical utility of buccal swabs for severe acute respiratory syndrome Coronavirus 2 detection in Coronavirus disease 2019 – infected children	1. Time 2. Viral load	Infeasible method for diagnosis inchildren.
Case Series	Azzi et al. (2020)	Department of Medicine and Surgery, University of Insubria, Italy.	Saliva is a reliable tool to detect SARS-CoV-2	1. Time 2. Viral load 3. Different methods	An alternative method, further studies needed.
Comparative Study	Kim et al. (2020)	Chonnam National University Medical School, Republic of Korea.	Viral load kinetics of SARS-CoV-2 infection in saliva in Korean patients: a prospective multi-center comparative study	1. Time 2. Viral load 3. Different methods	Ineffective method.
Prospective Study	Byrne et al.(2020)	Liverpool School of Tropical Medicine, Liverpool, UK.	Saliva alternative to upper respiratory swabs for SARS-CoV-2 diagnosis	1. Time 2. Viral load 3. Different methods	Effective method.
Prospective Study	Barat et al.(2021)	National Institutes of Health, Bethesda, Maryland, USA.	Pooled saliva specimens for SARS-CoV-2 testing	1. Time 2. Viral load 3. Different methods	Effective method.
Cohort study	Procop et al. (2020)	Cleveland Clinic, Cleveland, Ohio, USA.	A direct comparison of enhanced saliva to nasopharyngeal swab for the detection of SARS-CoV-2 in symptomatic patients	1. Time 2. Viral load 3. Different methods	An alternative method (more effective inthe first few days).

To be continued...

Continuation of Table 1.

Cohort study	Contreras et al. (2020)	Instituto de Biotecnología Universidad Nacional Autónoma de México, Cuernavaca Morelos, México.	Saliva sampling and its direct lysis, an excellent option to increase the number of SARS-CoV-2 diagnostic tests in settings with supply shortages	1. Time 2. Viral load 3. Different methods	An alternative method (feasible in underdeveloped countries).
Cross-sectionalstudy	Pasomsub et al. (2021)	Faculty of Medicine Ramathibodi Hospital,Mahidol University, Bangkok, Thailand.	Saliva sample as a non-invasive specimen for the diagnosis of coronavirus disease 2019: a cross-sectional study	1. Time 2. Viral load 3. Different methods	An alternative method (in places withlimited resources).
Case Study	Yee et al. (2021)	Children's Hospital Los Angeles, Los Angeles,California, USA.	Saliva is a promising alternative specimen for the detection of SARS-CoV-2 in children and adults	1. Time 2. Viral load 3. Different methods	An alternative method (in cases where collection of samples fromthe nasopharyngeal area is contraindicated).
Case Report	Tajima et al. (2020)	Hamamatsu Medical Center, Japan.	A case report of SARS-CoV-2 confirmed in saliva specimens up to 37 days after on set: proposal of saliva specimens for COVID-19 diagnosis and virus monitoring	1. Time 2. Different methods	An effective and feasible method for initial diagnosis of the disease.
Comparative Study	Babady et al. (2020)	Memorial Sloan Kettering Cancer Center (MSKCC) in New York City.	Performance of severe acute respiratory syndrome Coronavirus 2 real-time RT-PCR tests on oral rinses and saliva samples	1. Time 2. Viral load 3. Different methods	Effective method.
Prospective cross-sectional study	Skolimowska et al. (2020)	Imperial College Health Care NHS Trust, London, UK.	Non-invasive saliva specimens for the diagnosis of COVID-19: caution in mild outpatient cohorts with low prevalence	1. Time 2. Viral load 3. Different methods	Complementary method (does not replace the nasal swab method).
Prospective cross-sectional study	Savela et al.(2021)	California Institute ofTechnology, 1200 E. California Blvd.,Pasadena, CA, USA.	SARS-CoV-2 is detectable using sensitive RNA saliva testing days before viral load reaches detection range of low-sensitivity nasal swab tests	1. Time 2. Viral load 3. Different methods	An alternative method.
Prospective Study	Echavarria et al. (2021)	University Hospital, Ciudad Autónoma de Buenos Aires, Buenos Aires, Argentina.	Self-collected saliva for SARS-CoV-2 detection: A prospective study in the emergency room	1. Time 2. Viral load 3. Different methods	An alternative method, further studies needed.
Observational study	Justo et al. (2021)	Federal University of SãoPaulo, Department of Medicine, São Paulo, SP,Brazil.	Comparison of viral load between saliva and nasopharyngeal swabs for SARS-CoV-2: the role of days of symptoms onset on diagnosis	1. Time 2. Viral load 3. Different methods	Effective method.
Cross-sectional study	Yokota et al. (2021)	Hokkaido University Faculty of Medicine, Sapporo, Japan.	Equivalent SARS-CoV-2 viral loads by PCR between nasopharyngeal swab and saliva in symptomatic patients	1. Time 2. Viral load 3. Different methods	An alternative method.
Paired cohort study	Guzmán-Ortizet al. (2021)	Hospital Infantil de México Federico Gómez, México City, México.	Sensitivity of the molecular test in saliva for detection of COVID-19 in pediatric patients with concurrent conditions	1. Time 2. Viral load 3. Different methods	An alternative method.

To be continued...

Continuation of Table 1.

Comparative Study	Güçlü et al.(2020)	Sakarya University Training and Research Hospital, Clinic of Emergency Medicine, Sakarya, Turkey.	Comparison of saliva and oro-nasopharyngeal swab sample in the molecular diagnosis of COVID-19	1. Viral load 2. Different methods	An alternative method.
Cohort study	Lazari et al. (2022)	GlycoProteomics Laboratory, Department of Parasitology, ICB, University of São Paulo, SP, Brazil.	MALDI-TOF mass spectrometry of saliva samples as a prognostic tool for COVID-19	1. Time 2. Viral load 3. Different methods	Effective method
Cohort study	Miller et al.(2021)	Department of Medicine, Columbia University Irving Medical Center, New York, New York, USA.	Oral microbiome alterations and SARS-CoV-2 saliva viral load in patients with COVID-19	1. Time 2. Viral load	An alternative method (as astrategy to help with transmission and possiblecomplications of the disease).
Comparative Study	Abasiyanik et al. (2021)	Institutional Review Board (IRB) of the University of Chicago, USA.	Sensitive detection and quantification of SARS-CoV-2 in saliva	1. Time 2. Viral load 3. Different methods	Effective, method.
Case Series	Jeong et al. (2020)	Department of Internal Medicine, Chungbuk National University College of Medicine and Medical Research Institute, Cheongju, Republic of Korea.	Viable SARS-CoV-2 in various specimens from COVID-19 patients	1. Time 2. Viral load 3. Different methods	Alternative method.
Cross-sectionalstudy	Li et al. (2021)	Republic of China.	Analysis of viral load in different specimen types and serum antibody levels of COVID-19 patients	1. Time 2. Viral load 3. Different methods	Ineffective method.
Cohort study	Yokota et al. (2021)	Department of Biostatistics, Hokkaido University Graduate School of Medicine, Sapporo, Japan.	Mass screening of asymptomatic persons for severe acute respiratory syndrome Coronavirus 2 using saliva	1. Time 2. Viral load 3. Different methods	An alternative method (indicated forasymptomatic patients).
Control Case Study	Savela et al. (2021)	California Institute of Technology, Pasadena, California, USA.	Quantitative SARS-CoV-2 viral-load curves in paired saliva and nasal swabs inform appropriate respiratory sampling site and analytical test sensitivity required for earliest viral detection	1. Time 2. Viral load 3. Different methods	Alternative method.
Randomized Clinical Trial	Carrouel et al.(2021)	University Claude Bernard Lyon 1, University of Lyon, Lyon, France.	Saliva quantification of SARS-CoV-2 in real-time PCR from asymptomatic or mild COVID-19 adults	1. Time 2. Viral load	An alternative method.
Cross-sectionalstudy	Esteves et al. (2022)	Universidade Católica Portuguesa, Faculty of Dental Medicine (FMD), Center for Interdisciplinary Research in Health (CIIS), Viseu, Portugal.	Population wide testing pooling strategy for SARS-CoV-2 detection using saliva	1. Time 2. Viral load 3. Different methods	Effective method.
Prospective Study	Mohd Thabitet al. (2021)	Infectious Disease Department, Sungai Buloh Hospital, Ministry of Health Malaysia, Malaysia.	Diagnostic accuracy of fresh drooled saliva for SARS-CoV-2 in travelers	1. Time 2. Viral load 3. Different methods	Complementary method (does not replace the nasal swab method).
Clinical trial	Schaaf et al. (2021)	Department of Biological Sciences, Olivet Nazarene University, Bourbonnais, Illinois, USA.	Routine, cost-effective SARS-CoV-2 surveillance testing using pooled saliva limits viral spread on a residential college campus	1. Time 2. Viral load	An alternative method (in places with limited resources).
Clinical trial	Callahan et al. (2021)	Department of Pathology, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA.	Saliva is comparable to nasopharyngeal swabs for molecular detection of SARS-CoV-2	1. Time 2. Viral load	Effective method.

To be continued...

Continuation of Table 1.

Comparative Study	Ota et al.(2021)	Department of Laboratory Medicine, Nagasaki University Hospital, Nagasaki, Japan.	Detection of SARS-CoV-2 using qRT-PCR in saliva obtained from asymptomatic or mild COVID-19 patients, comparative analysis with matched nasopharyngeal samples	1. Viral load 2. Different methods	Effective method.
Prospective Study	Carrouel et al.(2021)	Laboratory "Health Systemic Process", EA4129, University Lyon 1, 69008 Lyon, France.	Performance of self-collected saliva testing compared with nasopharyngeal swab testing for the detection of SARS-CoV-2	1. Time 2.Viral load 3. Different methods	Effective method.
Cohort study	Lopes et al. (2021)	Instituto de Hematologia Arthur de Siqueira Cavalcanti/Hemorio, RuaFrei Caneca, 8, Centro, Rio de Janeiro.	A large cohort study of SARS-CoV-2 detection in saliva: a non-invasive alternative diagnostic test for patients with bleeding disorders	1. Viral load 2. Different methods	An alternative method (indicated for asymptomatic patients).
Prospective Study	Mestdagh et al. (2021)	Biogazelle,* Zwijnaarde; the Department of Biomolecular Medicine.	Evaluating diagnostic accuracy of saliva sampling methods for severe acute respiratory syndromeCoronavirus 2 reveals differential sensitivity and association with viral load	1. Time 2.Viral load 3. Different methods	An alternative method (inasymptomatic cases, further studies needed).
Cross-sectionalstudy	Uddin et al. (2021)	Infectious Diseases Division, icddr,b, Dhaka, Bangladesh.	Diagnostic performance of self-collected saliva versus nasopharyngeal swab for the molecular detection of SARS-CoV-2 in the clinical setting	1. Time 2. Viral load 3. Different methods	An alternative method (firstdays after symptoms)
Comparative Study	Procop et al. (2020)	Pathology and Laboratory Medicine Institute, Cleveland Clinic, Cleveland, Ohio, USA.	A direct comparison of enhanced saliva to nasopharyngeal swab for the detection of SARS-CoV-2 in symptomatic patients	1. Viral load 2. Different methods	An alternative method (indicated for asymptomatic patients).
Clinical trial	Fougère et al. (2021)	Pediatric Infectious Diseases and Vaccinology Unit, Department Women-Mother-Child, Lausanne University Hospital, Lausanne, Switzerland.	Performance of RT-PCR on saliva specimens compared with nasopharyngeal swabs for the detection of SARS-CoV-2in children: a prospective comparative clinical trial	1. Viral load 2. Different methods	An alternative method.
Comparative clinical trial	Alemany et al.(2021)	Universitari Germans Trias i Pujol, Barcelona Institute for Global Health, Rosselló, Badalona, Spain.	Self-collected mid-nasal swabsand saliva specimens, compared with nasopharyngeal swabs, for SARS-CoV-2 detection in mild COVID-19 patients	1. Time 2.Viral load 3. Different methods	An alternative method (important incases of mass population testing).
Cross-sectionalstudy	Beyene et al. (2021)	Armauer Hansen Research Institute, Jumma Road ALERT Compound, P.O. Box address 1005, Addis Ababa, Ethiopia.	Saliva is superior over nasopharyngeal swab for detecting SARS-CoV-2 in COVID-19 patients	1. Time 2. Viral load 3. Different methods	Effective method.
Cohort study	Johnson et al. (2021)	Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, Minnesota, USA.	Saliva testing is accurate for early-stage and presymptomatic COVID-19	1. Viral load 2. Differentmethods	An alternative method (important incases of masspopulation testing).
Single-center cross-sectional study	Gupta et al. (2021)	Departments ofMedicine, Microbiology& Biostatistics, All India Institute of Medical Sciences, New Delhi, India.	Gargle lavage & saliva: feasible & cheaper alternatives to nasal & throat swabs for diagnosis of COVID- 19	1. Viral load 2. Different methods	An alternative method.
Comparative clinical trial	Alemany et al.(2021)	Universitari Germans Trias i Pujol, Barcelona Institute for Global Health, Rosselló, Badalona, Spain.	Self-collected mid-nasal swabsand saliva specimens, compared with nasopharyngeal swabs, for SARS-CoV-2 detection in mild COVID-19 patients	1. Time 2.Viral load 3. Different methods	An alternative method (important incases of mass population testing).

To be continued...

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Cohort study	Johnson et al. (2021)	Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, Minnesota, USA.	Saliva testing is accurate for early-stage and presymptomatic COVID-19	1. Viral load 2. Different methods	An alternative method (important in cases of mass population testing).
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Source: The authors.

Throughout the COVID-19 pandemic, several moments were experienced around the disease, such as greater knowledge about its pathophysiology, the emergence of vaccines, and oscillations in the incidence of new cases of the infection caused by SARS-CoV-2. However, the continued need for diagnostic methods for the understanding of epidemiological scenarios and, consequently, the elaboration of health strategies is fundamental.

The presence of SARS-CoV-2 in saliva can be understood by its affinity for Angiotensin Converting Enzyme -2 (ACE-2), TMPRSS2, and TMPRSS4 (Huang et al., 2021). These receptors can be found throughout the upper or lower respiratory tract (Xu, Li, Gan, Du & Yao, 2020; Yan et al., 2020; Matuck et al., 2021). Also, the oral cavity presents multiplesites susceptible to being infected by the virus, among them: the tongue, hard and soft palate, oral mucosa, and minor salivary glands (Zhong et al., 2020; Huang et al., 2021). Finally, as a warning of the constant virus replacement in the saliva is that the larger salivary glands such as the parotid, submandibular, and also the minor salivary glands are a reservoir for SARS-CoV-2 replication (Xu et al., 2020; Matuck et al., 2021).

In addition to the production of saliva in the oral cavity, it has been suggested that the morning collection of samples of this fluid in the oropharyngeal region may be more sensitive than the nasopharyngeal swab because it is suggested that individuals who sleep in the supine position favor the flow of secretions from the nasopharynx, as well as secretions from the lower airways with ciliary movements would move to the upper respiratory tract (Hung et al., 2020).

To screen for COVID-19 cases, the collection of nasopharyngeal biopsy material followed by quantitative analysis using RT-PCR is considered the gold standard (Heikkinen, Marttila, Salmi & Ruuskanen, 2002; Lee et al., 2021). Despite this designation, some negative points of this strategy can be considered, such as the need for training a team for the collections, their exposure to the risk of infection in pandemic periods with the scarcity of resources can occur the lack of swabs and PPE, cause discomfort to patients, be contraindicated in cases of coagulopathic or anti-coagulated and with significant nasal septal deviation (Kim et al., 2017; Li, Liu, Yu, S. L. Tang & Tang, 2020; Lippi, Simundic & Plebani, 2020; Sri Santosh, Parmar, Anand, Srikanth & Saritha, 2020; WHO, 2020).

In contrast, saliva is easy to obtained and can be collected by the patient him/herself, and it presents a complex mixture of salivary gland secretions, crevicular fluid, sputum, and airway sputum (Miller et al., 2010). It can also be used for the diagnosis of several oral or systemic pathologies such as dengue, chikungunya, Ebola,Zika and yellow fever, severe acute respiratory syndrome (SARS), and Middle East Respiratory Syndrome (MERS) (Niedrig, Patel, El Wahed, Schädler & Yactayo, 2018).

In the SARS-CoV-2 pandemic, several studies point to saliva as an alternative sample for COVID-19 diagnosis (Jamal et al., 2020; To et al., 2020; Wong et al., 2020; Zheng et al., 2020), which was similar to the results of our review (Babady et al., 2020; Byerne et al., 2020; Hung et al., 2020; To et al., 2020; Barat et al., 2021).

In hospitalized patients with up to one week of symptom onset where nasopharyngeal swab and morning saliva samples were collected simultaneously, the latter showed significantly higher sensitivity and viral load than the nasopharyngeal swab ($p<0.001$) (Beyene et al., 2021).

Another study of 70 hospitalized patients who performed self-collection of saliva with a concomitant collection of nasopharyngeal swabs by healthcare professionals demonstrated that the saliva sample showed higher sensitivity to SARS-CoV-2, higher positivity in samples between the first and fifth day and after 10 days of symptom onset when compared to the nasopharyngeal swab. Finally, the comparison of these two samples showed similarity in the behavior of viral load reduction in parallel with the reduction of clinical symptoms inpatients (Wyllie et al., 2020). In addition to applicability in symptomatic patients under hospital admission, the collection of salivary samples is effective in population studies. In mass testing in asymptomatic patients, it showed a sensitivity of 92% while nasopharyngeal swabs were 86%, however, both showed specificity greater than 99.9% (Yokota et al., 2021).

Despite numerous studies presenting the usefulness of salivary samples compared to the nasopharyngeal collection, in this review, three studies presented this biological fluid asineffective (Kam et al., 2020; Kim et al., 2020; Li et al., 2021). For Kam et al. (2020) saliva showed lower mean viral load values in pediatric patients, as well as substantial differences in mean cycle threshold (Ct) values compared to nasopharyngeal swab, suggesting it is not a good screening parameter in children, but the authors point out that the study sample contained 11 children.

In the study by Kim et al. (2020) with 15 children under admission in four different hospitals, saliva was shown to have similar threshold Ct values compared to nasopharyngeal swabs, but salivary sensitivity was lower to SARS-CoV-2, especially in the first five initial days of symptoms.

Finally, in the study by Li et al. (2021) with 37 hospital inpatients, nasopharyngeal, anal, salivary, blood, and urine swab samples were collected. In this case, oral fluid showed only 16.22% positivity of samples for viral RNA while nasopharyngeal and anal swabs were 54.05% and 24.32%, respectively. In this context, the three aforementioned papers suggest the trend that salivary samples have lower sensitivity for SARS-CoV-2 than nasopharyngeal swabs. Still, two of them involve pediatric patients, and the other is with adults; however, it is worth noting that the three papers have small samples and difficulties in composing a heterogeneity of the same about the severity of the cases.

This integrative review included several types of clinical studies and excluded reviews, contemplating studies from the beginning of the COVID-19 pandemic until March 2022. As limitations of this study, it could be highlighted the non-systematic character of this study and the absence of meta-analysis.

CONCLUSION

Saliva has proven to be a good option for the initial diagnosis of COVID-19, in 5-7 days after the contagion of the disease, and for follow-up/monitoring of patients. On the other hand, despite the limitations of the studies found, saliva sampling in pediatric patients suggests having low sensitivity.

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