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Original Article

Evaluating Saliva as a Diagnostic Tool for COVID-19 in Dental Settings: A Meta-Analysis of Saliva, Nasopharyngeal, and Serum Specimens

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ABSTRACT

COVID-19 testing uses different types of specimens, including nasopharyngeal swabs, saliva, and serum. While the nasopharyngeal swab (NPS) remains the gold standard for diagnosing COVID-19, its invasive nature can cause patient discomfort and requires trained personnel for sample collection. This study aimed to evaluate the effectiveness of nasopharyngeal, serum specimens, and saliva in detecting COVID-19 and to compare saliva with the other two methods. A systematic search was conducted following the PRISMA 2020 guidelines across PubMed, the Cochrane COVID-19 study register, and the Saudi Digital Library. The QUADAS-2 tool was used to assess study quality. The primary outcome measured the sensitivity and specificity of serum, saliva, and NPS, while the secondary outcome focused on comparing the diagnostic accuracy of saliva versus NPS and serum. Data were collected from 39 studies in 20 countries, analyzing 20,024 patients and 22,123 samples. Despite significant heterogeneity ($P < 0.001$), the meta-analysis revealed significant differences in sensitivity among all specimen types, especially between NPS and saliva. The area under the curve (AUC) values indicated a high diagnostic performance: serum (AUC = 1.00) showed the highest efficacy, followed by saliva (AUC = 0.97) and NPS (AUC = 0.94). These findings suggest that saliva presents a viable, non-invasive alternative for the diagnosis of COVID-19 with comparable reliability to NPS.

Keywords: COVID-19 nucleic acid testing, Nasopharyngeal, COVID-19 testing, COVID-19 serological testing, Saliva, Serum.

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Introduction

COVID-19 is an infectious disease caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was found in Wuhan first, China, in December 2019 and has since led to a global health crisis [1, 2]. On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a pandemic, and the virus continues to spread worldwide, with reports of second and potential third waves [1-3]. As of February 21, 2023, WHO has recorded 757,264,511 confirmed cases and 6,850,594 fatalities due to COVID-19 [4].

The virus primarily spreads through respiratory and salivary droplets, as well as direct contact with infected individuals. Aerosol transmission and fecal-oral routes have also been identified, along with indirect spread via fomites and surfaces [1, 3, 5-10].

Although nasopharyngeal swabs (NPS) remain the gold standard for COVID-19 diagnosis, proper sample collection requires trained professionals, making it resource-intensive and costly for healthcare systems. Furthermore, NPS collection is contraindicated for individuals with anticoagulant therapy, coagulopathy, or significant nasal septum deviation, limiting its widespread applicability [11]. Given these challenges, an alternative diagnostic method that is less invasive, cost-effective, and reduces exposure risks for healthcare workers is highly desirable [12-16].

Since antibodies' presence against SARS-CoV-2 has been found in the mouth, saliva-based testing has the potential to serve as a different sampling method for COVID-19 detection. In addition to being non-invasive, saliva testing offers a rapid and convenient approach to diagnosing the virus [17]. Several studies have investigated the diagnostic accuracy of saliva in comparison with serum-based tests and nasopharyngeal tests for COVID-19 detection [1, 5, 16]. It is essential to assess the overall effectiveness of these different testing methods, particularly in dental settings, where infection prevention and early detection are critical [18, 19]. The objective of this study was to compare the diagnostic performance of nasopharyngeal, serum specimens, and saliva in detecting COVID-19 and to determine the most efficient and patient-friendly testing method. Therefore, this systematic review focuses on evaluating the diagnostic reliability of saliva-based tests in contrast to nasopharyngeal swabs and serum-based testing for the identification of SARS-CoV-2.

Materials and Methods

This study was formally registered, and approval was obtained from the ethical committee to proceed with the research.

PICO-Based Research Question

The primary focus of this study was to determine whether saliva-based diagnostic tests are comparable serum-based to nasopharyngeal tests for COVID-19 detection.

PICO Framework for the Study

Population: Individuals who were screened, suspected, or confirmed to have COVID-19.

Intervention: Diagnostic testing for COVID-19 using saliva, nasopharyngeal, and serum specimens.

Comparator/Control: Reverse transcription polymerase chain reaction (RT-PCR) validation tests.

Outcome: Evaluation of sensitivity and specificity for each specimen type, including saliva, nasopharyngeal, and serum samples.

Data Extraction

Relevant data were extracted from three major databases: Saudi Digital Library, PubMed, and the Cochrane COVID-19 study register. The search was conducted using specific filters and keywords such as "COVID-19," "SARS-CoV-2," "saliva," "nasopharyngeal," "serum," and "COVID-19 testing." This systematic review followed the PRISMA 2020 guidelines ensuring a structured approach to data collection. The selected studies and registers covered research published between January 2020 and June 2021 (**Figure 1**).

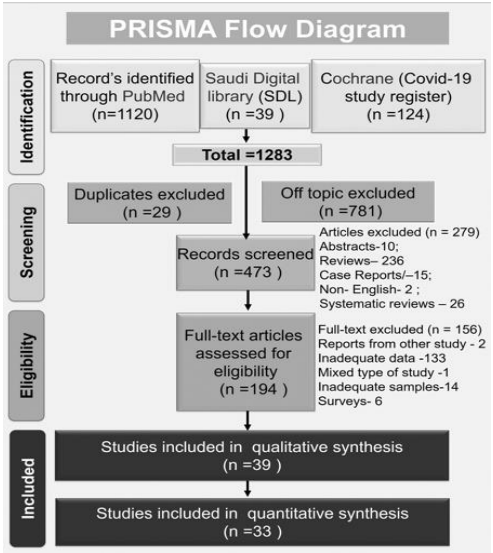


Figure 1. The PRISMA 2020 flow diagram, outlines the process of data search, screening, eligibility assessment, and final inclusion of studies for the systematic review and meta-analysis; this diagram integrates information from multiple databases and study registers to ensure a structured and transparent selection of

relevant research

Eligibility Criteria

Studies were selected based on specific inclusion and exclusion criteria. Articles that were duplicates, unrelated to the topic, written in languages other than English, or categorized as surveys, abstracts, case reports, systematic reviews, reviews, or meta-analyses were excluded. In contrast, studies that explicitly examined saliva, nasopharyngeal, and serum specimens from individuals who were screened, suspected, or diagnosed with SARS-CoV-2 were included. Only full-text articles published in English were considered, while studies with sample sizes below 50, those derived from other research, mixed-method studies incorporating questionnaires or reviews, and those with insufficient data were excluded.

Primary and Secondary Outcomes

The primary objective of this study was to evaluate the diagnostic accuracy of saliva, serum, and nasopharyngeal specimens by measuring their sensitivity and specificity. The secondary aim was to compare the diagnostic performance of saliva against nasopharyngeal and serum specimens in detecting COVID-19.

Risk of Bias Assessment

To assess the quality and reliability of the included studies, the QUADAS-2 tool [20, 21] was employed, which evaluates both the risk of bias and applicability concerns. Investigators were trained and calibrated by experienced specialist dentists familiar with similar research projects. Any discrepancies among the reviewers were resolved through mutual discussion until a consensus was reached [20].

Study Parameters

- Participants: Individuals, either symptomatic or asymptomatic, screened for, suspected of, or diagnosed with COVID-19.
- Index Tests: Diagnostic evaluation using saliva, nasopharyngeal, or serum specimens.
- Target Condition: Identification of SARS-CoV-2 infection.
- Reference Standard: RT-PCR (Reverse Transcriptase Polymerase Chain Reaction) nucleic acid assay.

Bias and Applicability Concerns

All four domains of risk of bias and three domains of applicability concerns were assessed using tailored questions to ensure a comprehensive evaluation. A study was classified as having a low risk of bias (green) if all signaling questions were answered "yes." If any question was answered "no," indicating a potential source of bias, it was categorized as a high risk of bias (red). If the available data were insufficient to determine the level of bias, the study was marked as unclear risk of bias (yellow). Similarly, applicability concerns were rated as low, high, or unclear, following the same classification approach.

Results and Discussion

Following the PRISMA 2020 guidelines (**Figure 1**), a total of 1,283 articles initially were identified. Among these, 1,120 were sourced from PubMed, 39 from the Saudi Digital Library (SDL), and 124 from the Cochrane COVID-19 study register. After removing 29 duplicate articles, 781 studies that were unrelated to COVID-19 testing or the specimen types under experiment were excluded. Additionally, 279 articles that met the exclusion criteria—such as non-English publications, abstracts, case reports, reviews, and systematic reviews or meta-analyses—were also removed.

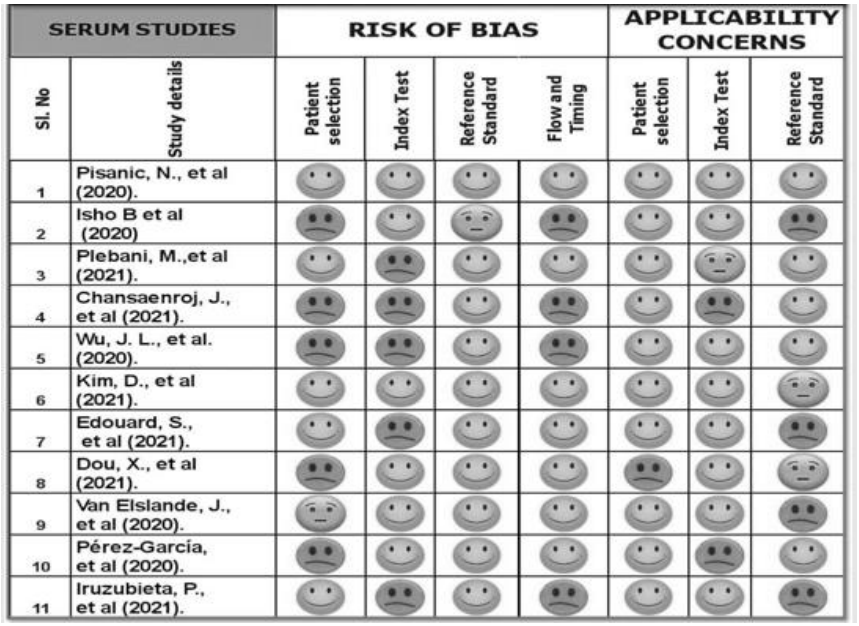
A total of 194 articles underwent a detailed eligibility screening. Based on the inclusion criteria, 39 studies were selected for quality assessment, while 6 studies qualified for quantitative synthesis. The entire selection process is illustrated in **Figure 2**.

SALIVA STUDIES		RISK OF BIAS				APPLICABILITY CONCERNS		
Sl. No	Study details	Patient selection	Index Test	Reference Standard	Flow and Timing	Patient selection	Index Test	Reference Standard
1	Procop, G. W., et al (2020).							
2	Pasomsub, E., et al (2021).							
3	Altawalah, H., et al (2020).							
4	Babady N.E.,et al (2021).							
5	Nagura-Ikeda, M., et al (2020).							
6	Rao, M., et al (2021).							
7	Vaz, S. N., (2020).							
8	Griesemer, S. B., et al (2021).							
9	Herrera, L. A.,et al (2021).							
10	Manabe, Y. C.,et al (2020).							
11	Jamal, A. J., et al (2021).							
12	Braz-Silva, P. H., et al (2020).							
13	Plantamura, J.,et al (2021). et al							
14	Amendola, A., et al (2021).							
15	Senok, A., et al (2020).							
16	Sutjipto, S., et al (2020).							
17	Jamal, A. J.,et al (2020).							
18	Sun, Q.,et al (2021).							
19	Ana Laura, G. O., et al (2021).							
20	Pisanic, N., et al (2020).							
21	Isho B et al (2020)							

a)

NASOPHARYNGEAL STUDIES		RISK OF BIAS				APPLICABILITY CONCERNS		
Sl. No	Study details	Patient selection	Index Test	Reference Standard	Flow and Timing	Patient selection	Index Test	Reference Standard
1	Rao, M., et al (2021).							
2	Jamal, A. J., et al (2021).							
3	Braz-Silva, P. H., et al (2020).							
4	Hirotsu, Y., et al . (2020).							
5	Toptan, T., et al (2021).							
6	Sutjipto, S., et al (2020).							
7	Jamal, A. J.,et al (2020).							
8	Sun, Q.,et al (2021).							

b)

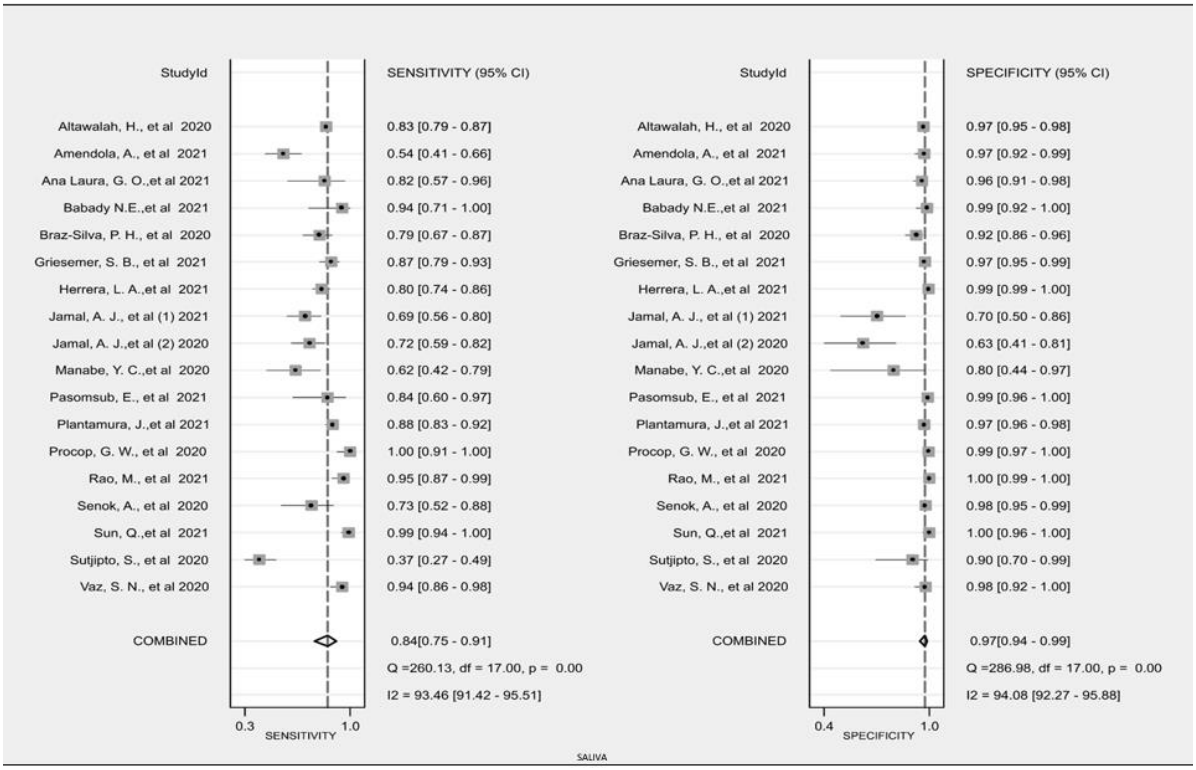


c)

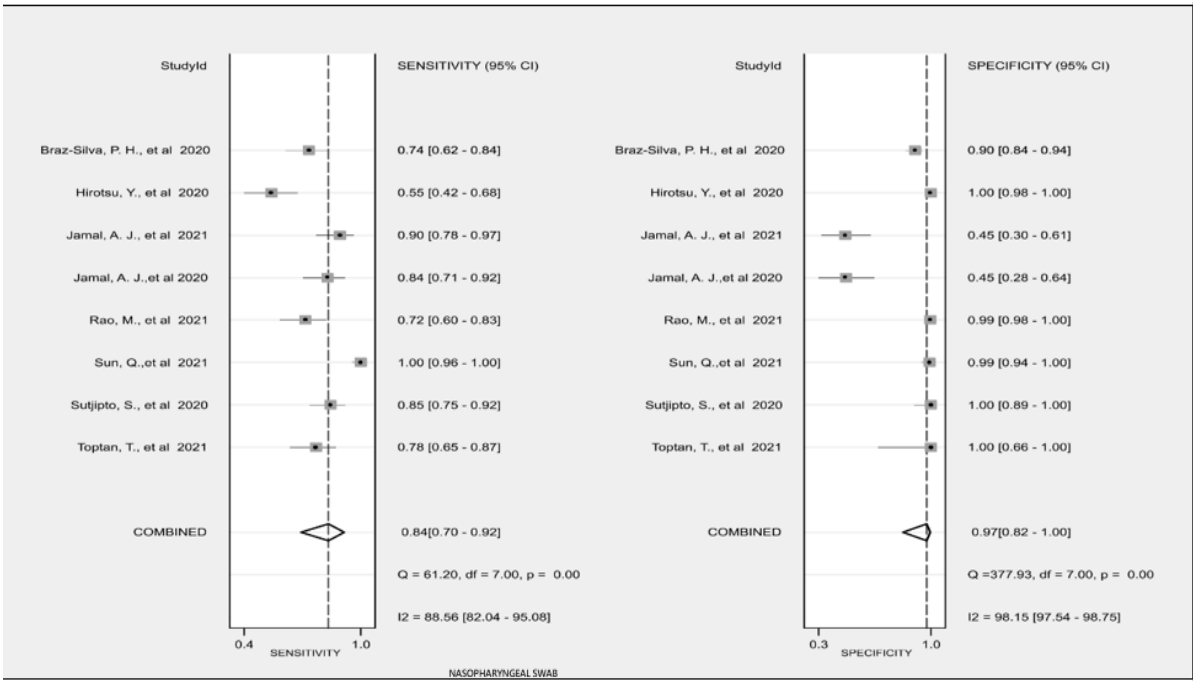
Figure 2. (a, b, and c): The quality assessment results of the studies using the QUADAS 2 tool for saliva (a), nasopharyngeal (b), and serum (c) specimens; the yellow color indicates an unclear risk of bias or applicability concern, red signifies a high risk of bias and applicability concern, and green represents a low risk of bias and applicability concern.

In this systematic review, 39 studies were included, covering twenty countries, 20,024 patients, and 22,123 samples. Further analysis was carried out on 33 studies that provided specific data on sensitivity and specificity for the specimens examined. The results of the sensitivity and specificity for serum specimens saliva and nasopharyngeal in the meta-analysis are displayed in the forest plots in **Figure 3**. **Table 1** demonstrates the evaluation of base data. **Table 2** provides an overview of the performance of the three specimen types under evaluation.

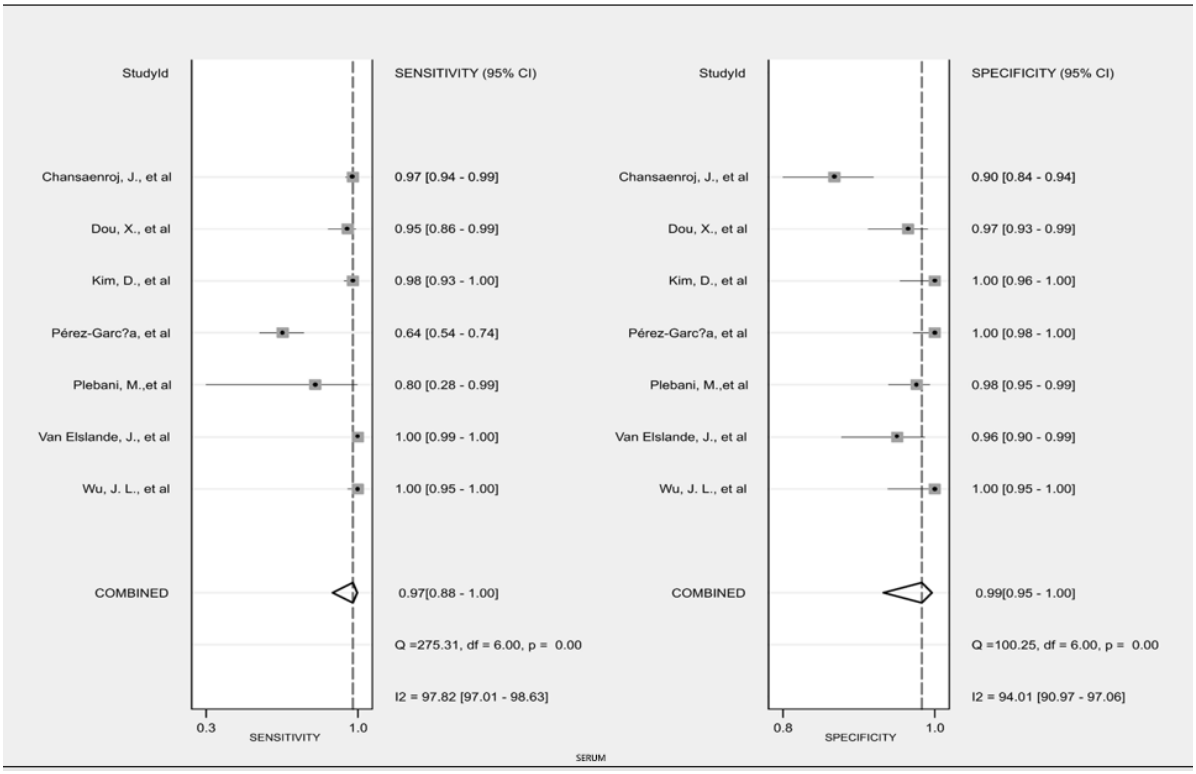
The positive likelihood ratio (PLR) for all specimens was greater than 1, indicating a higher probability of COVID-19 diagnosis in patients with positive test results. For saliva, the PLR was found to be 32.0 [14.0, 73.2], suggesting that individuals with a positive saliva test are 32 times more likely to test positive for the virus compared to healthy individuals. The negative likelihood ratio (NLR) for all tests was less than 1, meaning patients with negative results have a reduced likelihood of being infected. The NLR indicates that a lower percentage of true COVID-19 cases tested negative compared to those who tested negative and were not infected. Serum samples showed the lowest NLR, meaning they are the least likely to provide false negative results, making them the most reliable in this regard. The diagnostic odds ratio (DOR), which compares the likelihood of a positive result to a negative result, was highest for serum testing. This suggests that serum tests, particularly for active infections detected by IgG, offer the most effective method for COVID-19 diagnosis.


StudyId
SENSITIVITY (95% CI)
Altawalah, H., et al 2020 0.83 [0.79 - 0.87]
Amendola, A., et al 2021 0.54 [0.41 - 0.66]
Ana Laura, G. O.,et al 2021 0.82 [0.57 - 0.96]
Babady N.E.,et al 2021 0.94 [0.71 - 1.00]
Braz-Silva, P. H., et al 2020 0.79 [0.67 - 0.87]
Griesemer, S. B., et al 2021 0.87 [0.79 - 0.93]
Herrera, L. A.,et al 2021 0.80 [0.74 - 0.86]
Jamal, A. J., et al (1) 2021 0.69 [0.56 - 0.80]
Jamal, A. J.,et al (2) 2020 0.72 [0.59 - 0.82]
Manabe, Y. C.,et al 2020 0.62 [0.42 - 0.79]
Pasomsub, E., et al 2021 0.84 [0.60 - 0.97]
Plantamura, J.,et al 2021 0.88 [0.83 - 0.92]
Procop, G. W., et al 2020 1.00 [0.91 - 1.00]
Rao, M., et al 2021 0.95 [0.87 - 0.99]
Senok, A., et al 2020 0.73 [0.52 - 0.88]
Sun, Q.,et al 2021 0.99 [0.94 - 1.00]
Sutjipto, S., et al 2020 0.37 [0.27 - 0.49]
Vaz, S. N., et al 2020 0.94 [0.86 - 0.98]
COMBINED 0.84[0.75 - 0.91]
Q =260.13, df = 17.00, p = 0.00
I2 = 93.46 [91.42 - 95.51]
0.3
1.0
SENSITIVITY
StudyId
SPECIFICITY (95% CI)
Altawalah, H., et al 2020 0.97 [0.95 - 0.98]
Amendola, A., et al 2021 0.97 [0.92 - 0.99]
Ana Laura, G. O.,et al 2021 0.96 [0.91 - 0.98]
Babady N.E.,et al 2021 0.99 [0.92 - 1.00]
Braz-Silva, P. H., et al 2020 0.92 [0.86 - 0.96]
Griesemer, S. B., et al 2021 0.97 [0.95 - 0.99]
Herrera, L. A.,et al 2021 0.99 [0.99 - 1.00]
Jamal, A. J., et al (1) 2021 0.70 [0.50 - 0.86]
Jamal, A. J.,et al (2) 2020 0.63 [0.41 - 0.81]
Manabe, Y. C.,et al 2020 0.80 [0.44 - 0.97]
Pasomsub, E., et al 2021 0.99 [0.96 - 1.00]
Plantamura, J.,et al 2021 0.97 [0.96 - 0.98]
Procop, G. W., et al 2020 0.99 [0.97 - 1.00]
Rao, M., et al 2021 1.00 [0.99 - 1.00]
Senok, A., et al 2020 0.98 [0.95 - 0.99]
Sun, Q.,et al 2021 1.00 [0.96 - 1.00]
Sutjipto, S., et al 2020 0.90 [0.70 - 0.99]
Vaz, S. N., et al 2020 0.98 [0.92 - 1.00]
COMBINED 0.97[0.94 - 0.99]
Q =286.98, df = 17.00, p = 0.00
I2 = 94.08 [92.27 - 95.88]
0.4
1.0
SPECIFICITY
SALIVA

a)


StudyId
SENSITIVITY (95% CI)
Braz-Silva, P. H., et al 2020 0.74 [0.62 - 0.84]
Hirotsu, Y., et al 2020 0.55 [0.42 - 0.68]
Jamal, A. J., et al 2021 0.90 [0.78 - 0.97]
Jamal, A. J.,et al 2020 0.84 [0.71 - 0.92]
Rao, M., et al 2021 0.72 [0.60 - 0.83]
Sun, Q.,et al 2021 1.00 [0.96 - 1.00]
Sutjipto, S., et al 2020 0.85 [0.75 - 0.92]
Toptan, T., et al 2021 0.78 [0.65 - 0.87]
COMBINED 0.84[0.70 - 0.92]
Q = 61.20, df = 7.00, p = 0.00
I2 = 88.56 [82.04 - 95.08]
0.4
1.0
SENSITIVITY
StudyId
SPECIFICITY (95% CI)
Braz-Silva, P. H., et al 2020 0.90 [0.84 - 0.94]
Hirotsu, Y., et al 2020 1.00 [0.98 - 1.00]
Jamal, A. J., et al 2021 0.45 [0.30 - 0.61]
Jamal, A. J.,et al 2020 0.45 [0.28 - 0.64]
Rao, M., et al 2021 0.99 [0.98 - 1.00]
Sun, Q.,et al 2021 0.99 [0.94 - 1.00]
Sutjipto, S., et al 2020 1.00 [0.89 - 1.00]
Toptan, T., et al 2021 1.00 [0.66 - 1.00]
COMBINED 0.97[0.82 - 1.00]
Q =377.93, df = 7.00, p = 0.00
I2 = 98.15 [97.54 - 98.75]
0.3
1.0
SPECIFICITY
NASOPHARYNGEAL SWAB

b)



c)

Figure 3. Forest plots for the saliva studies (a), nasopharyngeal (NPS) studies (b), and serum studies (c)

Table 1. Statistical base data of studies

Study	TP	FP	FN	TN	Total
Saliva					
Altawalah *et al*. [22]	305	17	61	508	891
Amendola *et al.* [23]	36	3	31	99	169
Ana Laura *et al*. [24]	14	6	3	133	156
Babady *et al*. [25]	16	1	1	69	87
Braz-Silva *et al*. [26]	55	10	15	121	201
Griesemer *et al*. [27]	91	10	14	348	463
Herrera *et al*. [28]	139	10	34	1867	2050
Jamal *et al*. [29]	44	8	20	19	91
Jamal *et al*. [30]	46	9	18	15	88
Manabe *et al*. [31]	18	2	11	8	39
Pasomsub *et al*. [32]	16	2	3	179	200
Plantamura *et al*. [33]	180	29	25	971	1205
Procop *et al*. [34]	38	1	0	177	216
Rao *et al*. [35]	62	1	3	496	562
Senok *et al*. [36]	19	9	7	366	401
Sun *et al*. [37]	84	0	1	90	175
Sutjipto *et al*. [38]	31	2	52	19	104
Vaz *et al*. [39]	67	2	4	82	155
NPS					
Braz-Silva *et al*. [26]	52	15	18	131	216
Hirotsu *et al*. [40]	32	1	26	254	313
Jamal *et al*. [29]	44	23	5	19	91
Jamal *et al*. [30]	46	18	9	15	88
Rao *et al*. [35]	47	3	18	494	562

Sun *et al*. [37]	84	1	0	90	175
Sutjipto *et al*. [38]	62	0	11	32	105
Toptan *et al*. [41]	45	0	13	9	67
Serum					
Chansaenroj *et al*. [42]	187	19	5	164	375
Dou *et al*. [43]	57	4	3	141	205
Kim *et al*. [44]	127	0	3	100	230
Pérez-García *et al*. [45]	58	0	32	161	251
Plebani *et al*. [46]	4	4	1	207	216
Van Elslande *et al*. [47]	261	4	0	99	364
Wu *et al*. [48]	74	0	0	74	148

Table 2. Summary

Parameter	Saliva	NPS	Serum
Sensitivity	0.84 [0.75, 0.91]	0.84 [0.70, 0.92]	0.97 [0.88, 1.00]
Specificity	0.97 [0.94, 0.99]	0.97 [0.82, 1.00]	0.99 [0.95, 1.00]
Positive likelihood ratio	32.0 [14.0, 73.2]	28.0 [4.2, 189.4]	72.2 [18.2, 287.4]
Negative likelihood ratio	0.16 [0.10, 0.26]	0.17 [0.09, 0.32]	0.03 [0.01, 0.13]
Diagnostic odds ratio	199 [58, 687]	168 [22, 1281]	2827 [410, 19476]

The variability observed between the three specimen types—saliva, nasopharyngeal swabs (NPS), and serum—is highlighted by the statistical heterogeneity in the outcomes. **Table 3** presents the results of this variability. The null hypothesis assumes that all studies show consistent outcomes for COVID-19 detection, specifically for the identification of SARS-CoV-2. If the P-value from the chi-square test is greater than 0.1 ($P > 0.1$), it would support the null hypothesis. But, as indicated in **Table 3**, a P-value of less than 0.0001 ($P < 0.0001$) points to significant heterogeneity across the outcomes of the COVID-19 tests. The inconsistency index (I2), which measures heterogeneity, is over 50%, confirming the presence of substantial variability. As shown in **Table 3**, the heterogeneity across the studies varies significantly, with an I2 range of 96% to 99%, all with statistically significant P-values.

Table 3. Heterogeneity statistics for the performance of saliva, NPS, and serum specimens for COVID-19 testing; NPS = nasopharyngeal swab

Parameter	Measure	Saliva	NPS	Serum
Heterogeneity	Q	44.639	153.041	70.838
	df	2.00	2.00	2.00
	$P(x^2)$	< 0.0001	< 0.0001	< 0.0001
Inconsistency	I^2 [95%CI]	96 [92 - 99]	99 [98 - 99]	97 [95 - 99]

Fagan plots were used to assess how the diagnostic results from saliva, NPS, and serum samples affected the likelihood of a patient having COVID-19. Starting with an initial 25% probability of infection, the results indicated a significant increase in this probability to 91%, 90%, and 96% for saliva, NPS, and serum samples, respectively, when the test results were positive. Conversely, when the test results were negative, the probability of COVID-19 dropped from 25% to 5%, 5%, and 1% for saliva, NPS, and serum samples, respectively.

The summary receiver operating characteristic (SROC) curve, shown in **Figure 4**, demonstrates the pooled sensitivity of the three diagnostic tests. The ROC curve represents the likelihood of each specimen type detecting COVID-19, while the area under the curve (AUC) measures how well these tests can differentiate between positive and negative cases. The SROC-AUC model helps in comparing the diagnostic capability of each specimen for COVID-19 detection. The pooled sensitivity for saliva tests was found to be 0.84 (95% CI, 0.75 to 0.91), indicating a strong ability to identify positive SARS-CoV-2 cases. Additionally, the pooled specificity for saliva was 0.97 (95% CI, 0.94 to 0.99), reflecting the test's high accuracy in identifying COVID-19-negative patients. The AUC for saliva was 0.97 (95% CI, 0.95 to 0.98), highlighting the excellent performance of saliva tests in detecting the virus.

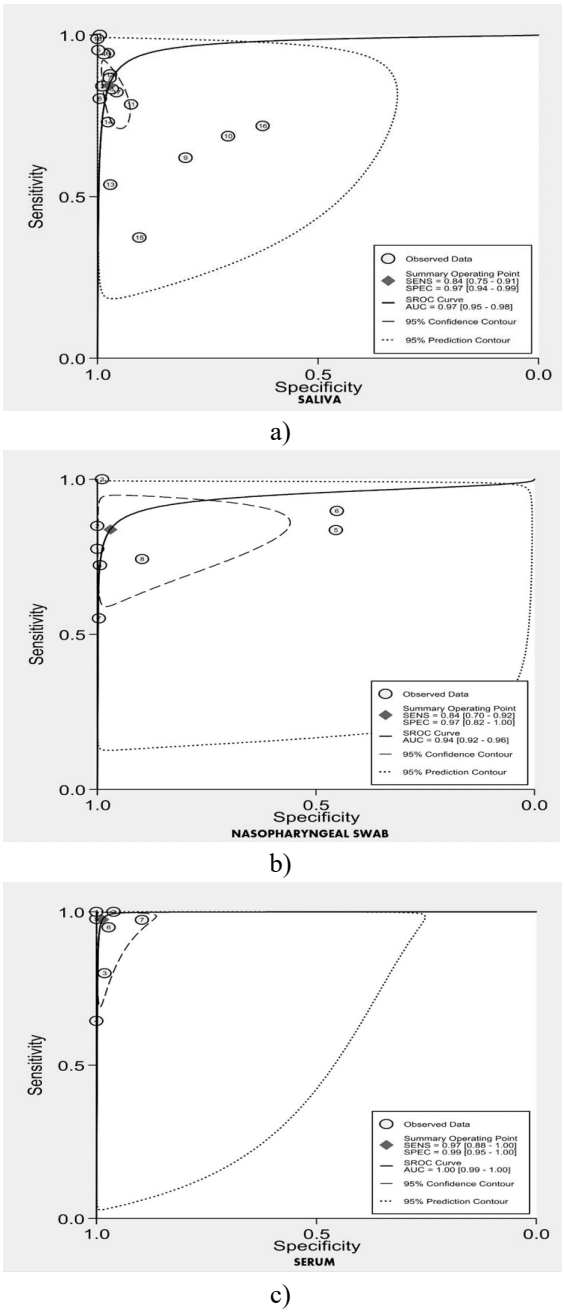


Figure 4. Summary receiver operating characteristic (SROC) curve; area under the curve (AUC) for saliva (a), NPS (b), and serum (c).

The analysis showed that NPS tests had a pooled sensitivity of 0.84 (95% CI, 0.70 to 0.92), indicating a strong ability to identify true positive SARS-CoV-2 cases. The specificity was 0.97 (95% CI, 0.82 to 1.00), suggesting it effectively distinguishes COVID-19-negative patients. The AUC value for NPS was 0.94 (95% CI, 0.92 to 0.96), signifying that NPS tests are highly reliable for detecting the virus.

Serum tests performed even better, with a pooled sensitivity of 0.97 (95% CI, 0.88 to 1.00), indicating excellent performance in detecting SARS-CoV-2. The pooled specificity was 0.99 (95% CI, 0.99 to 1.00), showing that it has an exceptional capacity to identify negative cases. The AUC for serum was 1.00 (95% CI, 0.95 to 0.98), highlighting its superior ability to detect the virus.

When comparing the three specimen types, serum samples exhibited the highest detection performance with a sensitivity of 0.97 (95% CI, 0.88 to 1.00), followed by saliva samples (0.84, 95% CI, 0.75 to 0.91) and NPS (0.84, 95% CI, 0.70 to 0.92). Serum also had the highest specificity estimate of 0.99 (95% CI, 0.95 to 1.00). However, it should be noted that the serum samples came from individuals suspected of or diagnosed with active COVID-19 infection. Importantly, none of the studies examined IgM, IgA, or IgG levels, with the focus being on IgG, which displayed the highest specificity, sensitivity, and overall detection performance.

The meta-analysis and systematic review aimed to assess the effectiveness of saliva-based COVID-19 testing for screening or remote testing, an option that doesn't require healthcare professionals for specimen collection. Saliva is a sample commonly handled by dental practitioners in their daily work, making its diagnostic accuracy particularly relevant for them. The analysis compared the diagnostic performance of three frequently used specimen types: saliva, nasopharyngeal swab (NPS), and serum.

NPS, a respiratory specimen, is widely recognized as the gold standard for SARS-CoV-2 detection and has been extensively used in COVID-19 testing and retesting [22, 23, 26, 29-32, 34-38, 40, 41, 49, 50]. However, studies focusing exclusively on NPS samples were less common [40, 41, 50-52]. There are several reasons why NPS, despite being the preferred choice, has some limitations. One issue is the variation in viral load at different stages of infection, which may result in lower viral loads during later stages, potentially leading to false-negative results [53]. Additionally, the test's reliability can be influenced by sample quality, which in turn depends on how well the patient follows collection instructions. Incorrect specimen collection techniques can also contribute to false negatives. Furthermore, research has shown that NPS testing conducted by trained professionals in hospital settings tends to yield more reliable results than tests conducted on outpatients or suspected cases [52]. NPS collection is also less well-tolerated by pediatric patients, though it remains recommended for those who are at higher risk, such as those with close contacts, epidemiological factors like infection clusters, or hospitalization requirements [54-60]. Complications, such as nasal bleeding, pain, or dislodgement of the swab have been reported with NPS

testing, some of which required medical interventions to resolve [61-67].

Serum samples can be analyzed for the presence of various immunoglobulins (Ig), including IgA, IgG, and IgM, which can be evaluated during different stages of infection and compared with other specimen types. These findings were cross-referenced with RT-PCR analysis, serving as the confirmatory test. Our study revealed that IgG exhibited higher specificity in symptomatic COVID-19 patients compared to those who were asymptomatic, and it provided more reliable results during active infection [42-48, 68-71]. This can be attributed to the seroconversion period, where severe cases of SARS-CoV-2 infection tend to show earlier seroconversion, leading to the development of elevated IgG levels, as compared to patients with mild symptoms. In some instances, measurable IgG antibodies might not be detectable, but the presence of neutralizing antibodies could indicate immunity [72, 73]. Variations in the frequency and timing of serum sample collection, as well as uncertainty regarding the precise onset of IgG response during seroconversion, may introduce confounding factors in the analysis. Although IgG levels can be a useful aid in assessing the status of active COVID-19 infection [74], serological tests with insufficient sensitivity and specificity are not recommended for confirming COVID-19 diagnosis [42-48, 68-73, 75-77]. Additionally, many studies lacked standardized methodologies for analyzing serological specimens, which could have led to over- or underestimation of the findings.

Saliva presents itself as a promising specimen for COVID-19 detection for several reasons. It contains epithelial cells from the oral cavity, which possess numerous angiotensin-converting enzyme 2 (ACE2) receptors. ACE2 is essential for SARS-CoV-2 entry into host cells, making saliva an ideal specimen for detecting the virus. For dental professionals, saliva is the most accessible sample for screening or diagnosing patients, as well as healthcare workers within or outside clinical settings [78]. Given that dental practice involves handling saliva, there is an unavoidable risk of SARS-CoV-2 transmission, both directly and indirectly. Therefore, dentists should take the necessary precautions to prevent contamination [26, 79, 80]. Saliva's ease of access makes it particularly advantageous in dental practice, where both asymptomatic and symptomatic COVID-19 patients pose a high risk of exposure. Access to saliva-based testing can help mitigate the spread of SARS-CoV-2 in dental environments.

SARS-CoV-2 can be present in saliva through three primary routes: (1) liquid droplets originating from both the upper and lower respiratory tracts, (2) gingival crevicular fluid derived from SARS-CoV-2-infected blood, and (3) salivary glands and their ducts [80, 81]. Studies have shown that ACE2 inhibitor levels in COVID-19 patients are higher in minor salivary glands compared to the lungs, which may explain why SARS-CoV-2 can be detected in asymptomatic individuals before any lung involvement is evident on radiologic imaging, further suggesting saliva as a possible source of viral transmission [82]. Detection of COVID-19 has been reported in both asymptomatic and symptomatic individuals [83-89]. Most studies collect saliva using one of three methods: saliva swabs, coughing up saliva, or directly from the salivary gland ducts [90]. However, our study found that the collection techniques were not standardized, which could potentially influence the results of the studies. It was identified that viral load in saliva fluctuated over time, with peak levels occurring early in the onset of symptoms, followed by a decline in viral load [72, 91].

Saliva presents a promising alternative to nasopharyngeal swabs (NPS) for COVID-19 testing, as NPS collection can be uncomfortable for patients and carries a risk of complications [92]. The need for trained professionals, personal protective equipment, and transportation of sample collection kits adds a logistical and financial burden, potentially hindering a country's economic growth. The use of self-collected saliva for large-scale screening, when proper collection methods are employed, could offer a practical solution to these challenges. False-negative results from NPS tests, even when administered by trained personnel, have highlighted the need for standardized procedures, calibration, and monitoring of the NPS technique. Such discrepancies have led to retesting, particularly when patients show symptoms indicative of COVID-19 [14, 93].

As the demand for COVID-19 testing and retesting continues to rise, alongside global regulations for quarantine, travel, and screening, saliva specimens have emerged as a convenient, non-invasive alternative for testing. Saliva collection presents no procedural discomfort, is suitable for both children and adults, has no contraindications for medically compromised patients, and yields comparable results to nasopharyngeal swabs (NPS). Many studies support the use of saliva for COVID-19 diagnosis, supporting its potential as an effective and user-friendly option [7, 14, 26, 72, 79, 83-91, 93-105].

Despite the huge volume of data available for saliva and NPS specimens, the study had certain limitations. A major challenge was the lack of standardized methodologies for data collection and statistical

analysis, making it difficult to retrieve consistent baseline data for performance evaluation. Multiple testing techniques were used, and variations in these methods influenced the outcomes, even though findings were confirmed with RT-PCR at different time points. The findings from the three specimens—saliva, NPS, and serum—are generally applicable, but the results from serum specimens should be interpreted with caution due to insufficient study data, particularly regarding the assessment of immunoglobulin levels during early and active stages of infection. Despite significant heterogeneity ($P < 0.001$), saliva specimens were found to have strong diagnostic efficacy for detecting COVID-19 and can be considered a reliable alternative for COVID-19 testing.

Conclusion

In conclusion, our review and meta-analysis demonstrate that saliva is a reliable specimen for detecting COVID-19, with results comparable to the gold standard nasopharyngeal swabs (NPS). NPS specimens, however, would be collected with care by trained professionals to minimize complications and ensure accurate diagnosis. Serum specimens, specifically for SARS-CoV-2 IgG, are effective in detecting active COVID-19 in symptomatic patients but would not be used as the sole diagnostic tool.

Saliva collection is non-invasive, easy to perform, and does not require professional training, leading to higher patient acceptance and making it safe for use in children. Self-administration of saliva tests can be conducted at home or in healthcare settings, making it particularly advantageous for the elderly, medically compromised individuals, and those on anticoagulants. These tests hold promise as point-of-care diagnostics and can be easily used by dental healthcare providers, allowing for convenient COVID-19 screening without the need for referrals. Saliva-based testing also has great potential for widespread use in business, social, educational, and entertainment settings as we move toward a post-pandemic normal.

Future research should focus on standardizing collection techniques, identifying the most effective saliva collection method for COVID-19 testing, and evaluating its diagnostic reliability for point-of-care use.

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