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The use of salivary specimen for COVID-19 detection using RT-PCR assay: a systematic review

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ABSTRACT

As coronavirus disease 2019 (COVID-19) cases arose globally, active case finding by performing throat swab test proposed high risk for the healthcare workers. Saliva had recently been reported to show positive detection means for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and proposed advantages of self-collection, less requirement of transport media, and reduced nosocomial transmission risk. However, support evidence regarding its diagnostic value was still lacking and varied widely in specimen collection method. This systematic review aimed to assess the diagnostic value of salivary specimens (SS) for COVID-19 detection using reverse transcription polymerase chain reaction (RT-PCR) assay compared with throat swab specimens (TSS), while putting into consideration confounders such as patients' initial condition, specimen collection method, and transport media used. Six databases were used for identifying relevant studies. Final search yielded 19 eligible studies which was reviewed based on the major outcome: diagnostic agreement, sensitivity & specificity, and viral load comparison. The use of SS as an alternative to TSS showed to be promising although specimen collection method needed to be standardized. SS was comparable to TSS in detecting COVID-19 using RT-PCR assay, especially in symptomatic or confirmed cases. More Randomized controlled trials (RCTs) were still needed to clearly demonstrate the ability of SS to capture asymptomatic cases in the setting of mass surveillance, where patients would self-collect the specimen at ease.

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1. INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a huge disease burden globally [1]–[3]. As new variants of SARS-CoV-2 arise, increased numbers of infection and deaths at unprecedented rate are being recorded worldwide [4]–[7]. Reinfection cases were not uncommon [8]–[11], even after COVID-19 vaccination program are being rolled out in many countries [12], [13]. Active case finding through contact tracing and performing testing are mandatory to prevent mass transmission since many active cases are asymptomatic [14]–[16]. Several methods have been proposed to provide early detection of COVID-19, i.e., through detection of viral ribonukleat acid (RNA) [17], [18], viral antigen [19], [20], and serum antibody [21], [22]. Viral RNA detection using nucleic acid amplification test (NAAT) is known to have low limit of detection with excellence analytical specificity and among many different types of NAATs, reverse transcriptase

polymerase chain reaction (RT-PCR) assay has been considered as the golden standard test for laboratory diagnosis of SARS-CoV-2 infection [23].

Throat swab specimens (TSS), which includes nasopharyngeal swabs (NPS), oropharyngeal swabs (OPS), dan naso-oropharyngeal swabs (NOS) are widely used and recommended as a standard specimen for the respiratory virus diagnosis, including SARS-CoV-2 [24]. However, performing throat swabs requires specific skills. In the setting of mass surveillance and the need for serial examinations, it would be nonbeneficial for the healthcare workers who are involved. Another issue of specimen collection device shortage due to high load of swab examinations calls for new means of COVID-19 specimen collection which requires simpler procedure and less expensive specimen collection devices.

Using salivary specimens (SS) for SARS-CoV-2 detection provides new interest as saliva has recently been reported to show positive detection means for SARS-CoV-2 [25], [26]. Some advantages of using SS for SARS-CoV-2 diagnosis are multiple specimens self-collection and reduced need for healthcare professional during specimen handling, which reduced nosocomial transmission risk [24]. Saliva collection method also reduces discomfort in serial examination caused by repetitive swabbing procedure as well as provides less requirements for transport medium due to specimen stability [27], [28]. However, aside from the advantages shown by this means of specimen collection, support evidence regarding its diagnostic value is still limited and varied. Different literatures showing distinct SS collection methods provided different results in comparison to TSS as the standard reference. We conducted a systematic review of literatures reporting the use of saliva as a specimen for RT-PCR assay in detecting SARS-CoV-2 in comparison to TSS, while taking into consideration the various methods used for SS collection.

2. RESEARCH METHOD

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) Guideline for reporting systematic reviews were used as general guide to conduct this systematic review [29]. The research question for this study is "How is the diagnostic value of salivary specimens for COVID-19 detection using RT-PCR assay compared with throat swab specimens?"

Six databases were used for identifying relevant studies, which consisted of Scopus, ProQuest, ScienceDirect, CINAHL, EBSCO, and PubMed. English articles were included and reviewed by three independent researchers. The terms used as keywords were saliva, salivary, COVID, SARS-CoV-2, detection, diagnosis, diagnostic, and RT-PCR. Inclusion criteria included studies between year 2020 and 2021 which evaluated the diagnostic value of SS examined using RT-PCR assay in comparison to any form of TSS (NPS, OPS, or NOS) for SARS-CoV-2 detection. Both published and unpublished studies (if any) were included. Study designs were all observational (cross-sectional, prospective, and retrospective study, if any). Exclusion criteria included studies which did not use RT-PCR assay for reference testing; studies which used specimens other than TSS as comparators; and study protocols and conference abstract, of which full text articles were not available online. Outcome measure was the diagnostic value of SS RT-PCR assay in comparison to TSS, included but not limited to diagnostic agreement, sensitivity, specificity, and viral load comparison denoted in form of cycle threshold (Ct) value.

All studies were critically appraised using methodological quality assessment tools specific to each study design. The AXIS critical appraisal tool for cross-sectional studies [30] was used for appraising observational cross-sectional studies. The Newcastle-Ottawa quality assessment form for cohort studies was used for appraising cohort studies. Data and information collected from the reviewed studies were aggregated and reported in narrative manner.

3. RESULTS AND DISCUSSION

We found 228 non-duplicated records from six different databases. Preliminary screening excluded 195 records, yielded a total of 33 records to be assessed for their eligibility through full text. A total of 14 records were further excluded due to unsuitable article types (review articles, letters to editors, and research proposal) and different study objectives, resulted in 19 records which were included within the final review as shown in Figure 1.

3.1. Participants and study characteristics

The 19 articles included in this review consisted of 13 cross-sectional studies [31]–[43] and six cohort studies [44]–[49] where specimens were collected and/or tested repetitively following certain period of time to obtain comparative results on different symptom onset duration. A total number of 8,227 participants were included within these studies. Most of the participants were adults with age ranging from 18-82 years old, except for four studies [35], [39], [40], [44] which also included pediatric patients (age four years and above).

All studies were comparing the diagnostic value of SS SARS-CoV-2 RT-PCR results with any forms of TSS (NPS, OPS, and/or NOS). Several studies were also comparing SARS-CoV-2 RT-PCR results from other respiratory tract specimens such as tracheal aspirate and sputum [45], cerumen and tears [34], and nasal swabs [47], [48] in additions to SS.

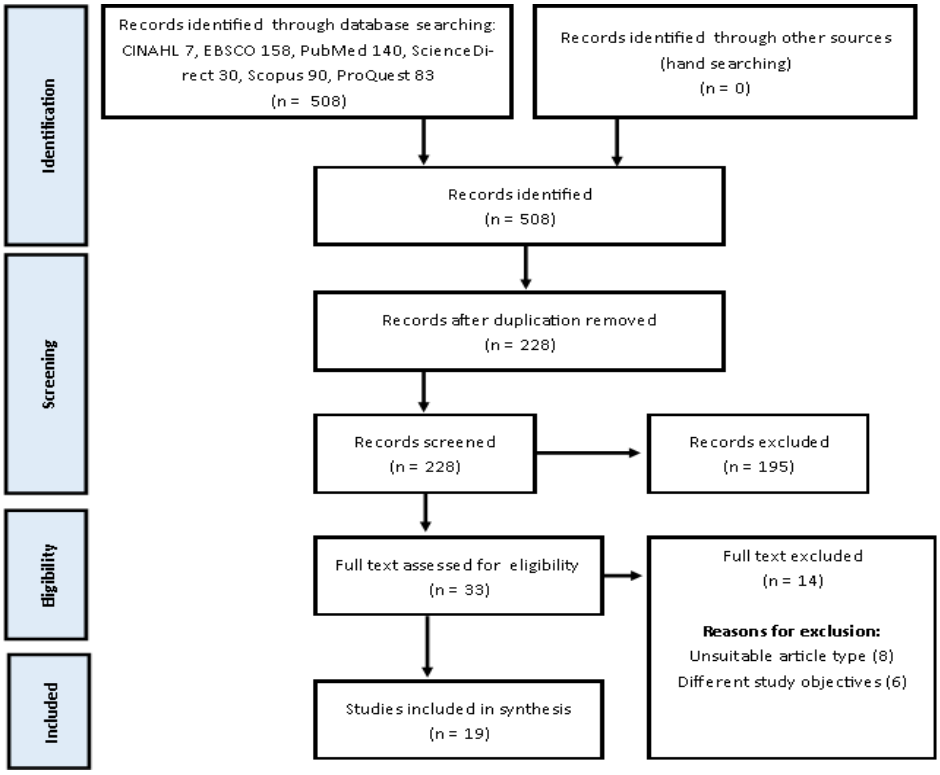


Figure 1. PRISMA flowchart of screened and included studies

3.2. Quality assessment

The 13 cross-sectional studies were appraised using the AXIS critical appraisal tool for cross-sectional studies, yielding fairly good quality. Four studies were considered to have less appropriate study design to meet the study objective by not providing control group to their study population [34], [35], [42], [43], eleven studies were unable to provide complete information regarding non-responder or missing data [31]–[36], [38]–[41], [43], and five studies were unable to provide information regarding ethical approval and/or may have possible conflict of interest [31], [32], [37], [38], [41].

The six remaining cohort studies were assessed using Newcastle-Ottawa quality assessment form for cohort studies. All six studies showed poor quality due to inability to provide information regarding comparability. No information was provided regarding control of confounding factors. Furthermore, four [44], [46], [47], [49] out of six studies included only confirmed case of COVID-19, provided no negative cases as non-exposed group. Among these six studies, only one study [47] denoted independent blind assessment of the outcome, while the other five provided no information at all.

3.3. Diagnostic agreement comparison between SS and TSS

All 19 studies included within this review showed similar characteristics in comparing performance of SS to TSS in detecting COVID-19 using SARS-CoV-2 RT-PCR assay. Each study may be unique in presenting the outcome, yet still comparable to each other. We grouped studies with similar outcome indicator to be reviewed together based on the diagnostic agreement, sensitivity and specificity, also viral load comparison.

We found 13 studies measured percent agreement between SS SARS-CoV-2 RT-PCR assay and TSS. Variations occurred between SS collection methods, which provided different types of SS collected and viral or universal transport media used, with additional information on patients' clinical condition (symptomatic or asymptomatic). This information is summarized in Table 1.

Table 1. Level of agreement shown in individual studies

Author	Type of SS collected	Transport media	Clinical condition	Percent agreement	Cohen's kappa coefficient (κ) for OA	Level of agreement
[31]	Induced by coughing	No	Symptomatic	PPA 100%. NPA 99.4%	NA	Strong
[32]	Pure, by spitting	UTM	Symptomatic	PPA 84.8%. NPA 97.8%. OA 94.4%	0.851 (95% CI, 0.745-0.958)	Strong
[33]	Induced by coughing	VTM	Symptomatic	PPA 83.43%. OA 91.25%	0.814 (95% CI, 0.775-0.854)	Strong
[34]	No detailed information	VTM	Both	PPA 76.3%	NA	Moderate
[35]	Pure, by spitting	No	Both	PPA 90.56%	NA	Strong
[36]	Pure, by drooling	No	Symptomatic	PPA 81.1%. NPA 99.8%	NA	Strong
[37]	No detailed information	No	Both	OA 98.4%	0.91 (95% CI, 0.82-0.96)	Strong
[39]	Pure, using nylon swab	VTM	Both	PPA 26.3%. OA 55%	0.252 (95% CI, 0.09-0.42)	Weak
[40]	Pure, by chewing cotton pad	No	Symptomatic	OA 83.6%	0.58 (95% CI)	Weak
[41]	No detailed information	No	Symptomatic	PPA 98%. OA 98.3%	0.96 (95% CI, 0.92-0.99)	Strong
[44]	Pure, by spitting	No	Symptomatic	OA 86.7% to 96.4%	0.625-0.883 (95% CI)	Moderate
[45]	Pure, by spitting	No	Symptomatic	PPA 60%	NA	Weak
[48]	Enhanced, by clearing throat and nose	No	Both	OA 76.2% (CDC-LDT). 80.1% (Fortitude 2.1)	0.537 (95% CI) (CDC-LDT). 0.602 (95% CI) (Fortitude 2.1)	Weak

NA=not available, UTM=universal transport media, VTM=viral transport media, PPA=positive percent agreement, NPA=negative percent agreement, OA=overall agreement.

Of all 13 studies showing percent agreement results, eight studies provided information regarding overall agreement (OA) with Cohen's kappa Coefficient (κ). Among these studies, only four studies [32], [33], [37], [41] showed strong to almost perfect agreement ($0.80 \leq \kappa \leq 1$). Study conducted by Uwamino *et al.* [44] showed moderate agreement ($0.60 \leq \kappa \leq 0.79$) for specimens collected long after symptom onset, but showed strong agreement for specimens collected within ten days of symptom onset. The other three studies [39], [40], [48] showed weak agreement ($0.40 \leq \kappa \leq 0.59$). Five remaining studies provided information regarding positive percentage agreement (PPA) with/without negative percentage agreement (NPA). Strong agreement was shown by three [31], [35], [36] out of the five studies, assuming less than 20% disagreement (PPA>80%) was considered sufficient [50]. Of all 13 studies included, only five studies included asymptomatic cases, of which two showed weak agreement [39], [48] and one showed moderate agreement [34].

We put into account the difference between studies regarding the means of SS collection method, the use of transport media, and patients' clinical condition. The idea of proposing SS as diagnostic specimen for COVID-19 detection laid on its simple specimen collection method, specimen stability without transport media, and aim for mass surveillance especially for asymptomatic cases. Induced saliva provided more complex procedure and might mask the study results as lower respiratory tract fluid might contaminate the SS. The use of transport media (UTM or VTM) omitted the initial purpose of using SS to resolve issue of transport media shortage. Study conducted by López-Martínez *et al.* [27] indicated the viral genome is stable and endures perturbations within saliva as biofluid. Included only symptomatic cases as study population might also mask the ability of SS to detect asymptomatic cases in the setting of mass or serial surveillance as in healthcare workers.

Considering only the pure (not induced or enhanced) saliva without the use of transport media to achieve the aim of this SS collection method, there are only four studies to compare. Three studies showed moderate [44] to strong [35], [36] agreement with one study showed weak [45] agreement. Note that from these four studies, only one study [35] included asymptomatic cases and still showed strong agreement. Compared to induced or enhanced saliva and/or the use of transport media, the number of studies showing moderate to strong agreement was higher than the number of studies showed weak agreement. This proposed that simpler method of SS collection can still be carried out with considerable similar result to TSS, although this was limited to symptomatic condition only.

3.4. Sensitivity and specificity comparison of SS and TSS

Ten studies provided information regarding sensitivity (with/without specificity) of SS SARS-CoV-2 RT-PCR assay in comparison to TSS. Table 2 summarized variation of results between studies. Of all eleven studies, four studies showed higher sensitivity of SS compared with TSS [37], [38], [40], [42], one of which showed significant difference [42] and the other showed concordant results in terms of sensitivity. Four studies showed lower sensitivity of SS [32], [34], [47], [49], all of which showed concordant results in terms of sensitivity, meaning no significant difference. Study conducted by Dogan *et al.* [43] performed serial specimen collection within four days (day 1 and day 5), resulted in significant difference in sensitivity on day 1, but with nonsignificant difference on day 5. Study conducted by Bidkar *et al.* [39] denoted significantly lower positivity rate of SS compared to the conventional NOS standards. This was consistent with κ value of 0.252 (95% CI, 0.09-0.42) which showed weak agreement.

Table 2. Sensitivity (SN) and specificity (SP) shown in individual studies

Author	SN & SP of SS	SN & SP of throat swab specimens	Additional information
[32]	SN 85.7% (95% CI, 70.6%-93.7%)	SN NPS 94.3% (95% CI, 81.4%-99.0%)	κ=0.851 (95% CI, 0.745-0.958)
[33]	SN 83.43% (95% CI, 79.07-87.20) SP 96.71% (95% CI, 94.85-98.04 %)	NA	κ=0.814 (95% CI, 0.775-0.854)
[34]	SN 76.3% (95% CI)	NA	PPA 76.3%
[37]	SN 93% (95% CI, 0.81-0.99)	SN NPS 91% (95% CI, 0.79-0.98)	κ=0.91 (95% CI, 0.82-0.96)
[38]	SN 53.7% (95% CI)	SN NPS 47.4% (95% CI)	p=0.13
[39]	SN 24.4% (95% CI). SP 94.9% (95% CI)	NA	κ=0.252 (95% CI, 0.09-0.42). p=0.002
[40]	SN 78.6% (95% CI, 67.6%-86.6%)	SN NOS 74.2% (95% CI, 63.7%-83.1%)	κ=0.58 (95% CI)
[42]	SN 88.09% (95% CI)	SN 45.24% (95% CI)	p<0.001
[43]	SN 63% (95% CI). day 1 SN 55% (95% CI). day 5	SN NPS and NOS both 83% (95% CI). day 1 SN NPS 55% (95% CI). SN NOS 60% (95% CI). day 5	p<0.001. day 1. p=0.386. day 5
[47]	SN 37.5% (95% CI, 24.2%-53.0%) SP 94.1% (95% CI, 73.0%-99.0%)	SN NPS 100% (95% CI, 91.2%-100.0%) SP 52.9% (95% CI, 31.0%-73.8%)	κ=0.225 (95% CI, 0.067-0.383)
[49]	SN 64% (95% CI)	SN NPS/OPS 77% (95% CI)	p=0.135

NA=not available

In terms of sensitivity, although some studies showed variability, only few proposed significant differences or diagnostic disagreement. Note that most of the studies used κ value to show agreement in comparing sensitivity and not p value to show significance. Diagnostic agreement does not always mean the SS are comparable to TSS in detecting COVID-19. κ value is affected by the probability for the condition to be present [51]. For most of these studies, the probability was quite high since most of the studies included COVID-19 confirmed or symptomatic suspected cases which later turned out to be confirmed case. However, these studies managed to indicate that SS was comparable to TSS in terms of sensitivity, especially in symptomatic or confirmed cases.

3.5. Viral load comparison between SS and TSS

Thirteen studies provided information regarding viral load (denoted as Ct value) of each specimen in comparison, i.e., SS and TSS. Table 3 summarized results variation between studies. Of all 13 studies, Ct values of SS were consistently higher than Ct value of TSS. Not all studies provided p value for comparisons, but the seven studies showed significant differences between these specimens' Ct value, meaning the detected viral load within SS was lower than TSS. Ct value of RT-PCR represents the number of amplification cycles required for the target gene to exceed a threshold level, meaning it inversely related to viral load [52]. Specimen quality and specimen handling affected the viral load detected within specimen. Note that SS are intended to be self-collected to provide ease of specimen collection. Standard procedure for SS collection should be made clear to ensure there are enough viral components within the specimen to be detected. On the other hand, further research setting should accommodate less manipulated SS (i.e., by induced cough, or chewing, or swabbing mucosal surface) to provide the closest expected diagnostic value of the simpler method of SS collection.

Table 3. Viral load (Ct value) shown in individual studies

Author/Year/Country	Form of Ct value	Ct value of SS	Ct value of TSS	Difference and/or p-value
[31]	Mean (SD)	24.16 (4.80)	20.55 (5.36)	-3.61 (95% CI, -5.78 to -1.44; p=0.002)
[32]	Median (IQR)	24.27 (23.46 to 24.96)	22.63 (21.88 to 23.85)	p=0.0331
[33]	Median difference	NA	NA	p<0.05
[34]	Mean (SD)	30.97 (1.56)	27.98 (4.29)	p<0.001
[35]	Mean (SD)	30.64 (2.83)	27.80 (3.44)	p=0.016
[36]	Median (IQR)	31 (29-37)	26 (21-34)	p<0.001
[37]	Median difference	Higher than the NPS	NA	2.76 (95% CI, 0.36-5.15; p=0.03)
[39]	Median	27.6 for E gene. 27.1 for ORF1ab	22.5 for E gene. 27.2 for ORF1ab	
[41]	Median (IQR)	26.10 (22.75-30.06)	18.88 (15.60-23.58)	p<0.0001
[42]	Mean difference	Higher than the throat swabs	NA	p<0.05
[45]	Median (IQR)	28.00 (20.08-31.00)	25.50 (17.37-36.74)	p<0.05
[47]	Median	35.34 (95% CI, 29.89-38.01)	33.65 (95% CI, 23.16-38.54)	NA
[49]	Median (IQR)	32 (23-38)	33 (27-35)	p<0.753

NA=not available

3.6. Strengths and limitations

This study pointed out the differences between patients' initial condition (symptomatic or asymptomatic), specimen collection method, and transport media used. To our knowledge, this was the first study considering all these parameters as confounders of the studies' aim, i.e., to provide alternative specimens to TSS which enabled ease specimen collection method, required less transport media, and enabled early detection of asymptomatic cases. Limitations of this study included limited number of studies which included asymptomatic cases and authors' limitation to further perform meta-analysis regarding the diagnostic accuracy.

4. CONCLUSION

The use of salivary specimens (SS) as an alternative to throat swab specimens (TSS) is promising although improvement in specimen collection method should be put into account. SS is comparable to TSS in detecting COVID-19 using RT-PCR assay. However, evidence of its comparability to TSS in asymptomatic cases is very much lacking since most of the studies included only symptomatic, suspected, or confirmed cases only. More RCTs are still needed to clearly demonstrate the ability of SS to capture asymptomatic cases in the setting of mass surveillance, where patients would self-collect the specimen at ease.

REFERENCES

[1] L. McArthur, D. Sakthivel, R. Ataide, F. Chan, J. S. Richards, and C. A. Narh, "Review of burden, clinical definitions, and management of Covid-19 cases," *American Journal of Tropical Medicine and Hygiene*, vol. 103, no. 2, pp. 625–638, 2020, doi: 10.4269/ajtmh.20-0564.

[2] L. E. Miller, R. Bhattacharyya, and A. L. Miller, "Spatial analysis of global variability in covid-19 burden," *Risk Management and Healthcare Policy*, vol. 13, pp. 519–522, 2020, doi: 10.2147/RMHP.S255793.

[3] K. Okunade, "January-March 2018 An Official Publication of The National Postgraduate Medical College of Nigeria," *Nigerian Postgraduate Medical Journal*, vol. 27, no. January, pp. 19–26, 2018, doi: 10.4103/npmj.npmj.

[4] W. T. Harvey *et al.*, "SARS-CoV-2 variants, spike mutations and immune escape," *Nature Reviews Microbiology*, vol. 19, no. 7, pp. 409–424, 2021, doi: 10.1038/s41579-021-00573-0.

[5] S. Saha *et al.*, "New waves, new variants, old inequity: A continuing COVID-19 crisis," *BMJ Global Health*, vol. 6, no. 8, pp. 1–6, 2021, doi: 10.1136/bmjgh-2021-007031.

[6] G. Gonzalez-Parra, D. Martínez-Rodríguez, and R. Villanueva-Micó, "Impact of a New SARS-CoV-2 Variant on the Population: A Mathematical Modeling Approach," *Mathematical and Computational Applications*, vol. 26, no. 2, p. 25, 2021, doi: 10.3390/mca26020025.

[7] R. Challen, E. Brooks-Pollock, J. M. Read, L. Dyson, K. Tsaneva-Atanasova, and L. Danon, "Risk of mortality in patients infected with SARS-CoV-2 variant of concern 202012/1: Matched cohort study," *The BMJ*, vol. 372, 2021, doi: 10.1136/bmj.n579.

[8] F. Zare *et al.*, "COVID-19 reinfection in Shahroud, Iran," *Epidemiology & Infection*, vol. 149, pp. 1–12, 2021.

[9] J. Zhang *et al.*, "COVID-19 reinfection in the presence of neutralizing antibodies," *National Science Review*, vol. 8, no. 4, pp. 4–9, 2021, doi: 10.1093/nsr/nwab006.

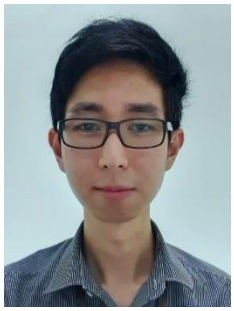
[10] K. K.-W. To *et al.*, "Coronavirus disease 2019 (COVID-19) Re-infection by a phylogenetically distinct severe acute respiratory syndrome coronavirus 2 strain confirmed by whole genome sequencing," *Clinical Infectious Diseases*, vol. 73, no. 9, pp. e2946–e2951, 2021, doi: 10.1093/cid/ciaa1275.

[11] B. Garduño-Orbe *et al.*, "Sars-cov-2 reinfection among healthcare workers in mexico: Case report and literature review,"

Medicina (Lithuania), vol. 57, no. 5, 2021, doi: 10.3390/medicina57050442.
[12] J. Wang, C. Kaperak, T. Sato, and A. Sakuraba, "COVID-19 reinfection: A rapid systematic review of case reports and case series," *Journal of Investigative Medicine*, vol. 69, no. 6, pp. 1253–1255, 2021, doi: 10.1136/jim-2021-001853.
[13] L. Lo Muzio, M. Ambosino, E. Lo Muzio, and M. F. A. Quadri, "Sars-cov-2 reinfection is a new challenge for the effectiveness of global vaccination campaign: A systematic review of cases reported in literature," *International Journal of Environmental Research and Public Health*, vol. 18, no. 20, 2021, doi: 10.3390/ijerph182011001.
[14] C. P. Muller, "Do asymptomatic carriers of SARS-COV-2 transmit the virus?," *The Lancet Regional Health - Europe*, vol. 4, p. 100082, 2021, doi: 10.1016/j.lanepe.2021.100082.
[15] G. Syangtan *et al.*, "Asymptomatic SARS-CoV-2 carriers: a systematic review and meta-analysis," *Frontiers in Public Health*, vol. 8, no. January, pp. 1–10, 2021, doi: 10.3389/fpubh.2020.587374.
[16] M. Alene *et al.*, "Magnitude of asymptomatic COVID-19 cases throughout the course of infection: A systematic review and meta-analysis," *PLoS ONE*, vol. 16, no. 3 March, pp. 1–12, 2021, doi: 10.1371/journal.pone.0249090.
[17] R. Verna *et al.*, "Analytical performance of covid-19 detection methods (Rt-pcr): Scientific and societal concerns," *Life*, vol. 11, no. 7, pp. 1–17, 2021, doi: 10.3390/life11070660.
[18] L. Jones *et al.*, "Isothermal amplification and fluorescent detection of SARS-CoV-2 and SARS-CoV-2 variant virus in nasopharyngeal swabs," *PLoS ONE*, vol. 16, no. 9 September, 2021, doi: 10.1371/journal.pone.0257563.
[19] L. E. Brümmer *et al.*, *Accuracy of novel antigen rapid diagnostics for SARS-CoV-2: A living systematic review and meta-analysis*, vol. 18, no. 8. 2021.
[20] E. Schuit *et al.*, "Diagnostic accuracy of rapid antigen tests in asymptomatic and presymptomatic close contacts of individuals with confirmed SARS-CoV-2 infection: Cross sectional study," *The BMJ*, vol. 374, 2021, doi: 10.1136/bmj.n1676.
[21] S. A. Ejazi, S. Ghosh, and N. Ali, "Antibody detection assays for COVID-19 diagnosis: an early overview," *Immunology and Cell Biology*, vol. 99, no. 1, pp. 21–33, 2021, doi: 10.1111/imcb.12397.
[22] A. P. Espejo *et al.*, "Review of current advances in serologic testing for COVID-19," *American Journal of Clinical Pathology*, vol. 154, no. 3, pp. 293–304, 2020, doi: 10.1093/AJCP/AQAA112.
[23] P. Garneret *et al.*, "Performing point-of-care molecular testing for SARS-CoV-2 with RNA extraction and isothermal amplification," *PLoS ONE*, vol. 16, no. 1 January, 2021, doi: 10.1371/journal.pone.0243712.
[24] R. C. Medeiros da Silva, L. C. Nogueira Marinho, D. N. de Araújo Silva, K. Costa de Lima, F. Q. Pirih, and A. R. Luz de Aquino Martins, "Saliva as a possible tool for the SARS-CoV-2 detection: A review," *Travel Medicine and Infectious Disease*, vol. 38, no. August, 2020, doi: 10.1016/j.tmaid.2020.101920.
[25] C. Chaimayo *et al.*, "Rapid SARS-CoV-2 antigen detection assay in comparison with real-time RT-PCR assay for laboratory diagnosis of COVID-19 in Thailand," *Virology Journal*, vol. 17, no. 1, Dec. 2020, doi: 10.1186/s12985-020-01452-5.
[26] N. N. Y. Tsang, H. C. So, K. Y. Ng, B. J. Cowling, G. M. Leung, and D. K. M. Ip, "Diagnostic performance of different sampling approaches for SARS-CoV-2 RT-PCR testing: a systematic review and meta-analysis," *The Lancet Infectious Diseases*, vol. 21, no. 9, pp. 1233–1245, 2021, doi: 10.1016/S1473-3099(21)00146-8.
[27] B. López-Martínez *et al.*, "Saliva as a promising biofluid for SARS-CoV-2 detection during the early stages of infection," *Boletin Medico del Hospital Infantil de Mexico*, vol. 77, no. 5, pp. 228–233, 2020, doi: 10.24875/BMHIM.20000204.
[28] N. E. Babady *et al.*, "Performance of Severe Acute Respiratory Syndrome Coronavirus 2 Real-Time RT-PCR Tests on Oral Rinses and Saliva Samples," *Journal of Molecular Diagnostics*, vol. 23, no. 1, pp. 3–9, Jan. 2021.
[29] M. J. Page *et al.*, "Cohort 22 Clinical Research: Surgical Approaches 1," *Nihon Bika Gakkai Kaishi (Japanese Journal of Rhinology)*, vol. 59, no. Supplement, pp. S59–S61, 2020, doi: 10.7248/jjrhi.59.s59.
[30] M. J. Downes, M. L. Brennan, H. C. Williams, and R. S. Dean, "Development of a critical appraisal tool to assess the quality of cross-sectional studies (AXIS)," *BMJ Open*, vol. 6, no. 12, 2016, doi: 10.1136/bmjopen-2016-011458.
[31] G. W. Procop *et al.*, "A Direct Comparison of Enhanced Saliva to Nasopharyngeal Swab for the Detection of SARS-CoV-2 in Symptomatic Patients," *Journal of Clinical Microbiology*, vol. 58, no. 11, Nov. 2020, doi: 10.1128/JCM.01946-20.
[32] M. L. Landry, J. Criscuolo, and D. R. Peaper, "Challenges in use of saliva for detection of SARS CoV-2 RNA in symptomatic outpatients," *Journal of Clinical Virology*, vol. 130, no. July, p. 104567, Sep. 2020, doi: 10.1016/j.jcv.2020.104567.
[33] H. Altawalah, F. AlHuraish, W. A. Alkandari, and S. Ezzikouri, "Saliva specimens for detection of severe acute respiratory syndrome coronavirus 2 in Kuwait: A cross-sectional study," *Journal of Clinical Virology*, vol. 132, Nov. 2020, doi: 10.1016/j.jcv.2020.104652.
[34] F. M. Hanege *et al.*, "SARS-CoV-2 Presence in the Saliva, Tears, and Cerumen of COVID-19 Patients," *Laryngoscope*, vol. 131, no. 5, pp. E1677–E1682, Oct. 2021, doi: 10.1002/lary.29218.
[35] E. E. Tutuncu, D. Ozgur, and M. Karamese, "Saliva samples for detection of SARS-CoV-2 in mildly symptomatic and asymptomatic patients," *Journal of Medical Virology*, vol. 93, no. 5, pp. 2932–2937, May 2021, doi: 10.1002/jmv.26821.
[36] B. Barat *et al.*, "Pooled saliva specimens for SARS-CoV-2 testing," *Journal of Clinical Microbiology*, vol. 59, no. 3, pp. 1–24, Mar. 2021, doi: 10.1128/JCM.02486-20.
[37] C. Kandel *et al.*, "Detection of sars-cov-2 from saliva as compared to nasopharyngeal swabs in outpatients," *Viruses*, vol. 12, no. 11, Nov. 2020, doi: 10.3390/v12111314.
[38] E. C. man Leung, V. C. ying Chow, M. K. ping Lee, and R. W. man Lai, "Deep throat saliva as an alternative diagnostic specimen type for the detection of SARS-CoV-2," *Journal of Medical Virology*, vol. 93, no. 1, pp. 533–536, Jan. 2021
[39] V. Bidkar, M. Mishra, N. Gade, and K. Selvaraj, "Conventional Naso-oropharyngeal sampling versus self-collected saliva samples in COVID-19 testing," *Indian Journal of Otolaryngology and Head and Neck Surgery*, 2021, doi: 10.1007/s12070-021-02571-3.
[40] P. H. Braz-Silva *et al.*, "Performance of at-home self-collected saliva and nasal-oropharyngeal swabs in the surveillance of COVID-19," *Journal of Oral Microbiology*, vol. 13, no. 1, 2021, doi: 10.1080/20002297.2020.1858002.
[41] M. Echavarria *et al.*, "Self-collected saliva for SARS-CoV-2 detection: A prospective study in the emergency room," *Journal of Medical Virology*, vol. 93, no. 5, pp. 3268–3272, May 2021, doi: 10.1002/jmv.26839.
[42] J. Fan *et al.*, "Hock-a-loogie saliva as a diagnostic specimen for SARS-CoV-2 by a PCR-based assay: A diagnostic validity study," *Clinica Chimica Acta*, vol. 511, pp. 177–180, Dec. 2020, doi: 10.1016/j.cca.2020.10.004.
[43] O. A. Dogan *et al.*, "Does sampling saliva increase detection of SARS-CoV-2 by RT-PCR? Comparing saliva with oro-nasopharyngeal swabs," *Journal of Virological Methods*, vol. 290, no. 1, p. 114049, Apr. 2021, doi: 10.1016/j.jviromet.2020.114049.
[44] Y. Uwamino *et al.*, "Accuracy and stability of saliva as a sample for reverse transcription PCR detection of SARS-CoV-2," *Journal of Clinical Pathology*, vol. 74, no. 1, pp. 67–68, Jan. 2021, doi: 10.1136/jclinpath-2020-206972.
[45] R. Can Sarinoglu, D. Guneser, B. Erturk Sengel, V. Korten, and A. Karahasan Yagci, "Evaluation of different respiratory samples

and saliva for the detection of SARS CoV-2 RNA," *Marmara Medical Journal*, vol. 34, no. 1, pp. 51–56, 2021.
[46] C. K. C. Lai *et al.*, "Prospective study comparing deep throat saliva with other respiratory tract specimens in the diagnosis of novel coronavirus disease 2019," *Journal of Infectious Diseases*, vol. 222, no. 10, pp. 1612–1619, Nov. 2020.
[47] Y. Tsujimoto *et al.*, "Diagnostic accuracy of nasopharyngeal swab, nasal swab and saliva swab samples for the detection of SARS-CoV-2 using RT-PCR," *Infectious Diseases*, vol. 53, no. 8, pp. 581–589, 2021, doi: 10.1080/23744235.2021.1903550.
[48] A. K. J. Teo *et al.*, "Saliva is more sensitive than nasopharyngeal or nasal swabs for diagnosis of asymptomatic and mild COVID-19 infection," *Scientific Reports*, vol. 11, no. 1, Dec. 2021, doi: 10.1038/s41598-021-82787-z.
[49] S. E. Kim *et al.*, "Viral Load Kinetics of SARS-CoV-2 Infection in Saliva in Korean Patients: a Prospective Multi-center Comparative Study," *Journal of Korean Medical Science*, vol. 35, no. 31, pp. 1–8, 2020, doi: 10.3346/jkms.2020.35.e287.
[50] M. L. McHugh, "Interrater reliability: The kappa statistic," *Biochemia Medica*, vol. 22, no. 3, pp. 276–282, 2012.
[51] A. Casagrande, F. Fabris, and R. Girometti, "Beyond kappa: an informational index for diagnostic agreement in dichotomous and multivalue ordered-categorical ratings," *Medical and Biological Engineering and Computing*, vol. 58, no. 12, pp. 3089–3099, 2020, doi: 10.1007/s11517-020-02261-2.
[52] S. N. Rao, D. Manissero, V. R. Steele, and J. Pareja, "A Narrative Systematic Review of the Clinical Utility of Cycle Threshold Values in the Context of COVID-19," *Infectious Diseases and Therapy*, vol. 9, no. 3, pp. 573–586, 2020,

BIOGRAPHIES OF AUTHORS



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