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Review article

Comparing saliva and nasopharyngeal swab specimens in the detection of COVID-19: A systematic review and meta-analysis

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Abstract *Background/purpose:* Due to the easy transmission of COVID-19, the virus is a threat to global health. Early diagnosis of suspected patients will play an essential role in preventing further spread of COVID-19. The aim of this review study was to evaluate saliva specimen in comparison to nasopharyngeal swab (NPS) specimen in studies selected from various databases.
Materials and methods: To achieve the objective of this study, a systematic literature search was carried out in four databases, namely PubMed, Google Scholar, Cochrane Library, and LILACS. The keywords ″COVID-19″, ″Nasopharyngeal Swab″, and ″Saliva″ were utilized via Boolean operators.
Results: 14 articles were included in this review study following the eligibility criteria. Based on data presented in studies used in the meta-analysis, there was no significant difference between both specimen types for detection of COVID-19. Heterogeneity test showed that I^2 value was 5.790% (<20%). The effect size (risk ratio) of the 14 studies was 0.951 (<1).
Conclusion: With the results revealing no significant difference between the two types of specimen in the diagnosis of COVID-19, the use of saliva specimen is preferable for widespread use because it is easily collected without the need for qualified health workers. However, more in vivo studies are required in order to compare and evaluate saliva and NPS specimens in detecting COVID-19 using various techniques.

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Introduction

The outbreak of a respiratory virus with unclear origin began in December 2019, in Hubei province, China, and soon posed a threat to global health due to its easy transmission. After extensive research on the virus, it was categorized as a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Later, in February 2020, the World Health Organization (WHO) named the virus ″Corona Virus Diseases 2019″ (COVID-19). To control the fast spread of the virus, various measures including social distancing and lockdowns were taken in many parts of the world, disrupting the living and working conditions of people.[1,2]

It is essential to find a safe and reliable diagnostic specimen type and its potential implication for detecting COVID-19, particularly in asymptomatic patients. SARS-CoV-2 has been detected in different specimens of human body, including saliva, nasopharyngeal or oropharyngeal swabs, blood, feces, urine, and tears, among which nasopharyngeal swab and saliva are more commonly used for the detection of COVID-19.[3–5]

Nasopharyngeal swabbing followed by real-time reverse transcription polymerase chain reaction (RT-PCR) technique is the best choice for detection of COVID-19.[4] Nonetheless, the collection of NPS specimen can cause the patient to cough, or bleed (especially in patients with thrombocytopenia), increasing the risk of transmitting the virus to healthcare workers. On the contrary, collecting saliva specimen decreases the possibility of exposing healthcare personnel to COVID-19 as it can be self-collected through spitting into a sterile bottle. Thus, saliva specimen can be used as an alternative for the detection of COVID-19.[6] Saliva is secreted by salivary glands and consists of proteins, peptides, and other molecular compounds which have various biological functions in the oral cavity. Saliva is considered as a diagnostic window for various pathologies diseases, particularly respiratory viruses such as COVID-19.[7] The aim of this review study was to evaluate saliva and NPS specimens in detecting COVID-19 using RT-PCR.

Material and methods

Literature search

Electronic literature search was carried out across PubMed, Cochrane Library, Google Scholar, and LILACS to find intended articles published from December 2019 to October 2020. The Boolean operators ″AND″ and ″OR″ were utilized for the following search keywords: COVID-19, nasopharyngeal swab, and saliva in various combinations. The search results were collected and imported into the reference manager of EndNote Software and duplicate papers were eliminated. It should be added that the data extraction was performed by two investigators.

PICO question is as follows:

Is the saliva sample a reliable diagnostic method (I) for the detection of COVID-19 (O) in patients (P) compared to the nasopharyngeal swab sample (C)?

Population: Patients.

Intervention: Saliva specimen.

Comparison: Nasopharyngeal swab specimen.

Outcome: Detection of COVID-19.

Inclusion criteria

The criteria for the inclusion of articles in this literature review:

1. Full text of articles written in English.
2. All papers published from December 2019 to October 2020.
3. In vivo studies.
4. Studies on the comparison between saliva (posterior saliva) and nasopharyngeal swab specimens for detecting COVID-19; the presence or absence of other specimens are not essential.

Exclusion criteria

The criteria for the exclusion of articles in this literature review:

1. Review studies.
2. Studies with unclear data.
3. Studies with no main results, including guidelines and recommendations.

Results

The initial search yielded 940 articles. After the removal of duplicates, 926 articles were screened by title, as a result of which 860 articles were excluded because they did not include a comparison between saliva and nasopharyngeal swab specimens. At the next stage, the abstracts of the remaining 66 articles were assessed, which resulted in the exclusion of 42 more articles for two reasons; 1. The studies focused on various diagnostic techniques rather than the efficacy of specimen types in detecting the virus. 2. The studies contained unclear data with regard to either the results or participants. It should be mentioned that out of the 66 articles, 7 articles were not accompanied with an abstract, so to examine them, the full texts were reviewed directly. Thus, 24 articles were included for the full-text review; in this process, 7 articles were discarded since they addressed a different PICO question or did not clearly answer the question. Further, in one article, the patients' participation was considerably higher than that of other studies, which led to an intervention in the analysis. And the other article showed no clear data in the final test. Also, the full text of one study was not available despite contacting the authors and requesting the full text. Therefore, at the end of the screening process, 14 articles met all the criteria and were included in the quantitative analysis.

Fig. 1 depicts the study selection process. Table 1 and Fig. 2 provide general information on the selected articles.[8–21] It needs to be clarified that in the studies by Jamal et al. and Williams et al. T (total number of patients participating in the study) in the meta-analysis and data visualisation is, in fact, the number of the participating

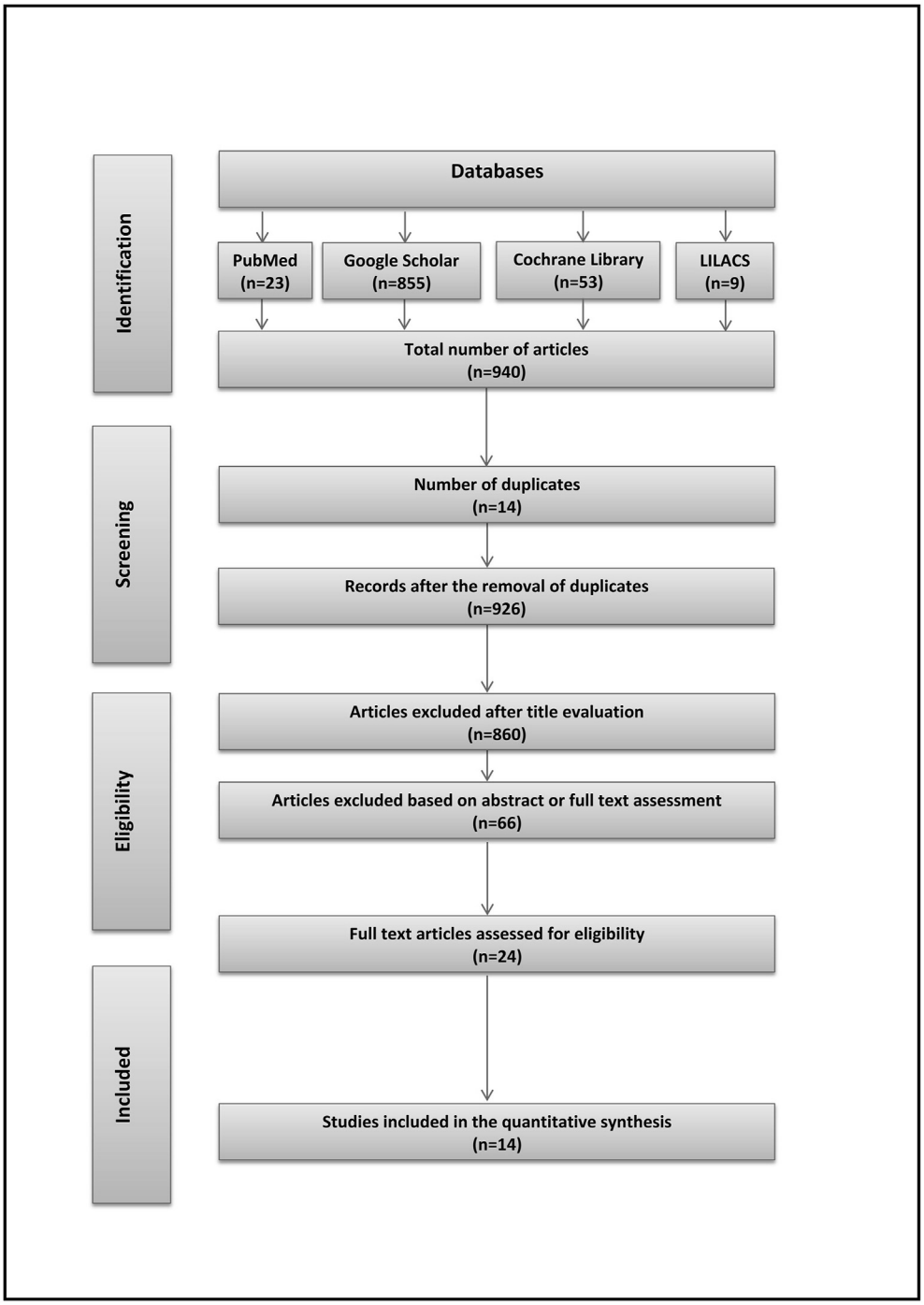

Figure 1 Flow chart of the screening process.

patients which were considered in the final analysis for detection of COVID-19.[9,14] In addition, due to unclear data on 8 patients in the study by Procop et al., 8 specimens were excluded from the final comparative analysis; therefore, the rest of participating patients were included in the meta-analysis and Fig. 2.[16]

Statistical heterogeneity test was assessed using the I^2 statistics. I^2 value showed 5.79% (<20%). P-value was 0.09 which is less than 0.1 (10%) and indicates that heterogeneity at 90% confidence interval was not statistically significant. Fig. 3 presents 14 included studies in the meta-analysis in which the risk ratio was selected as the effect size. The total effect size was 0.951 (<1), which means that based on data presented in studies used in the meta-analysis, saliva and NPS specimens had the same precision in detecting COVID-19.

Fig. 4 illustrates forest plot graphic representation of the results of the meta-analysis. Studies were grouped into two categories, namely group N (nasopharyngeal swab specimen) and group S (saliva specimen). Group N consists of the studies in which the number of patients that tested positive using NPS specimens was greater than the number

Table 1 General information on selected studies.

Study	Country	Patients		Sample Type	Method
		N (M/F)	Age Median		
Chen et al.	China	58 (28/30)	38	Saliva/NPS	RT-qPCR
Jamal et al.	Canada	91 (52/39)	66	Saliva/NPS	RT-qPCR
Kandel et al.	Canada	429 (−/−)	age > 18	Saliva/NPS	RT-qPCR
Landry et al.	USA	124 (−/−)	−	Saliva/NPS	RT-qPCR
Pasomsub et al.	Thailand	200 (69/131)	36	Saliva/NPS	RT-qPCR
Vaz et al.	Brazil	155 (46/109)	40	Saliva/NPS	RT-qPCR
Williams et al.	Australia	622 (−/−)	−	Saliva/NPS	RT-qPCR
Leung et al.	China	95 (−/−)	42	Saliva/NPS	RT-qPCR
Procop et al.	USA	224 (−/−)	44	Saliva/NPS	RT-qPCR
Sakanashi et al.	Japan	28 (−/−)	−	Saliva/NPS	RT-qPCR
Senok et al.	UAE	401 (329/72)	35.5	Saliva/NPS	RT-qPCR
Wyllie et al.	USA	70 (41/29)	61.4	Saliva/NPS	RT-qPCR
Yokota et al.	Japan	42 (25/17)	73	Saliva/NPS	RT-qPCR
Iwasaki et al.	Japan	76 (−/−)	69	Saliva/NPS	RT-qPCR

of patients that tested positive using saliva specimens. In contrast to group N, group S consists of the studies in which the number of patients that tested positive using saliva specimens was more than those tested using NPS specimens.

The overall risk ratio of group N and group S were 0.898 and 1.109, respectively. While the overall risk ratio for both groups (0.898 and 1.109) was nearly the same, the 95% confidence interval half width for group S (0.135) was nearly twice as group N (0.065). Therefore, it could be concluded that the dispersion in studies categorized as group S is greater than those categorized as group N. Since events and total data of the study by Iwasaki et al. were the same, the study was not included in the forest plot of meta-analysis in Fig. 4.[21]

Discussion

Real Time Polymerase Chain Reaction (RT-PCR) is the gold standard for the detection of SARS-CoV-2 infection from various clinical specimens.[22] However, the sensitivity and specificity of different RT-PCR kits are not 100% accurate. Many factors can affect the results, including the collection procedure, handling of material, and viral load of the sample (e.g., duration of symptoms and severity of disease).[23,24] The range of reported agreement or disagreement between saliva and NPS specimens as diagnostic specimen types in the detection of COVID-19 is different in studies.[25–27] Hence, this study aimed to compare saliva specimen with NPS specimen to identify which specimen type is reliable for the diagnosis of COVID-19. To do so, meta-analysis was employed to reach a comprehensive conclusion.

The use of saliva as a diagnostic tool for the detection of RNA viruses, such as ZIKA and Ebola viruses is well established.[28,29] Findings of previous studies reported satisfactory outcomes in the detection of SARS-CoV-1/2 RNA using saliva specimen.[30,31] Saliva specimen requires preparation prior to RNA extraction and getting the right volume is essential.[4] On the contrary, swabbing of the nasopharynx is done through the nasal cavity via palpation without direct visualization, which if performed incorrectly can lead to an increased false-negative result. Therefore, knowledge of the anatomy of the nasal cavity is essential for the health care personnel who perform this procedure.[32]

Quantitative analysis in the present review study revealed the same effect size for saliva and NPS specimens in detecting COVID-19 using RT-PCR, indicating that they can both detect the virus reliably. This finding is in agreement with that of previous studies.[4,25] Since both specimens have similar detection rate, the simplicity of the sample collection would be highlighted, meaning saliva sampling is not only easier but also safer. Moreover, the presence of trained healthcare workers to collect saliva specimen is not required.[33] To answer the PICO question, there is no significant difference between saliva and NPS specimens in detecting COVID-19 using RT-PCR technique. Nonetheless, using saliva specimen seems to be the better option due to its convenient and fast collecting.

The result of the viral culture of group S in Fig. 4 demonstrated that the viral load of SARS-CoV-2 was higher in saliva, which may be due to the fact that ACE-2 cells that cover the salivary gland ducts are the first target of SARS-CoV.[6,7] Hence, the viral load of SARS-CoV-2 might be higher in the salivary gland than in the nasopharynx. However, meta-analysis revealed that neither saliva nor NPS specimens are 100% sensitive in detecting COVID-19. It is suggested that in order to confirm diagnosis in suspected cases with a negative COVID-19 result, a combination of saliva and NPS specimens should be used.

In contrast to other review studies concerning SARS-CoV-2 which included only 5, 7, and 11 articles in the quantitative synthesis, our study utilized 14 articles to support the result and ensure a firm conclusion between saliva and NPS specimens in detecting COVID-19.[34–36] Moreover, since there is still limited data on COVID-19, this review study did not take other factors, such as other specimens and severity of disease or others diagnostic techniques into account. Further studies should address these issues.

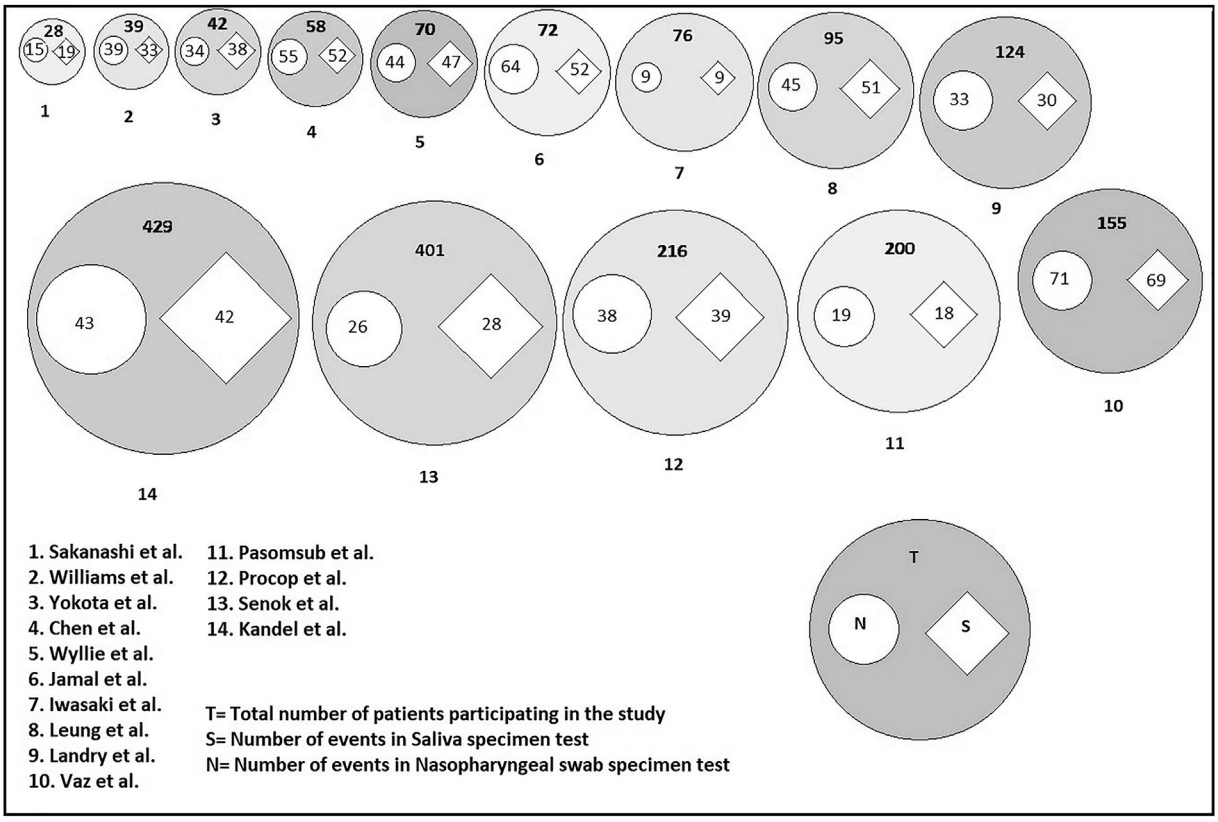

Figure 2 Data visualisation of selected studies.

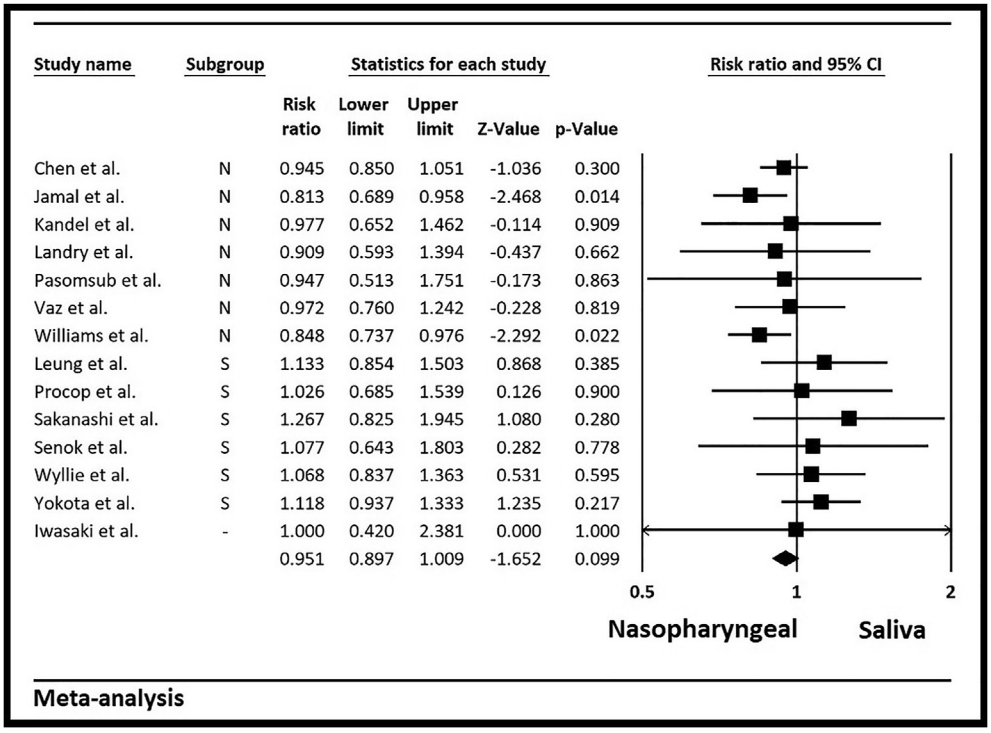

Figure 3 Blobbogram results of meta-analysis among 14 studies.

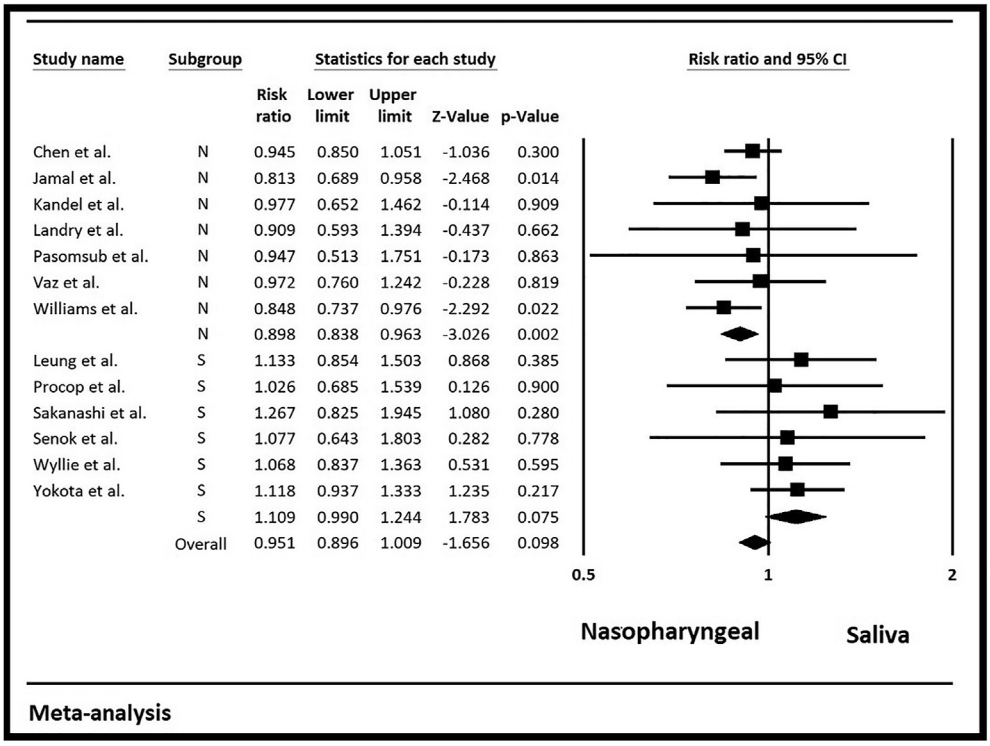

Figure 4 Blobbogram results of meta-analysis between two groups.

Based on the findings of this study, it can be concluded that the overall concordance of saliva and NPS specimens is the same for the detection of SARS-CoV-2 RNA using RT-PCR. However, saliva is suggested to be used as a non-invasive specimen providing satisfactory results in detecting COVID-19. Nonetheless, more data are needed to evaluate the sensitivity of saliva and NPS specimens in suspected patients.

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