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Diagnostic accuracy of fresh drooled saliva for SARS-CoV-2 in travelers

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ABSTRACT

Background: The standard for SARS-CoV-2 diagnosis is RT-PCR from nasopharyngeal or oropharyngeal swabs. Major airports require COVID-19 screening, and saliva has the potential as a substitute specimen for SARS-CoV-2 diagnosis. We investigated the utility of fresh drooled saliva against NPS for COVID-19 screening of travelers. Methods: We recruited 81 travelers and 15 non-travelers (including ten controls) prospectively within a mean of 3.22 days of RT-PCR confirmed COVID-19. Each study participant provided 2 mls of early morning fresh drooled whole saliva separately into a sterile plastic container and GeneFiX™ saliva collection kit. The saliva specimens were processed within 4 h and tested for SARS-CoV-2 genes (E, RdRP, and N2) and the results compared to paired NPS RT-PCR for diagnostic accuracy.

Results: Majority of travellers were asymptomatic (75.0%) with a mean age of 34.26 years. 77 travelers were RT-PCR positive at the time of hospitalization whilst three travelers had positive contacts. In this group, the detection rate for SARS-CoV-2 with NPS, whole saliva, and GeneFiX™ were comparable (89.3%, 50/56; 87.8%, 43/49; 89.6%, 43/48). Both saliva collection methods were in good agreement (Kappa = 0.69). There was no statistical difference between the detection rates of saliva and NPS (p > 0.05). Detection was highest for the N2 gene whilst the E gene provided the highest viral load (mean = 27.96 to 30.10, SD = 3.14 to 3.85). Saliva specimens have high sensitivity (80.4%) and specificity (90.0%) with a high positive predictive value of 91.8% for SARS-CoV-2 diagnosis.

Conclusion: Saliva for SARS-CoV-2 screening is a simple accurate technique comparable with NPS RT-PCR.

1. Introduction

Coronavirus Disease 2019 (COVID-19), was first reported in December 2019 as a cluster of pneumonia cases in Wuhan, China [1]. By March 2020, the World Health Organisation (WHO) declared COVID-19 a pandemic [1]. At the time of writing, over 187 million individuals have been infected by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19 [2]. Over 4 million people have died from the disease [2], and it has drastically changed social life and air travel.

The main mode of transmission of SARS-CoV-2 is via exposure to virus infected respiratory droplets from close contacts [3].

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may appear 2–14 days after the exposure, and depending on severity of presenting symptoms, individuals are classified as having asymptomatic or presymptomatic infection, mild illness, moderate illness, severe illness and critical illness [3]. Approximately 40%–45% of SARS-CoV-2 infection is asymptomatic nature and this poses significant challenges for the containment of COVID-19 [1,4]. However, it is undeniable that the categories for the severity of illness are different from other clinical guidelines and trials, and the variability of the clinical status of patients over time [3].

Current statistics describe the unprecedented levels of human travel impacted by the COVID-19 pandemic. Overall, the number of flights reported by The International Air Transport Association (IATA) showed a tremendous reduction from 38.9 million (2019) to 16.4 million (2020) [3]. This could be due to uncertainty whether air travel potentiates the risk of viral transmission, despite limited reports available. Modern aeroplanes are equipped with high-efficiency particulate air (HEPA) filters which help to minimize potential cabin contaminations [6]. However, there is still a minimal risk of infection in an enclosed cabin due to other factors leading to aerosol transmission such as source strength, duration of exposure and ventilation within the enclosed space [6]. Besides that, droplet transmission is possible when passengers have direct contact with respiratory droplets or contaminated surfaces [6]. On-board transmission reports have shown to be limited but there was isolated reported case SARS transmission where 29 probable on-board secondary cases were later traced to 40 flights [6]. Due to the severity of SARS-CoV-2, countries allowing air travel have started to implement strict standard operating procedures (SOPs) such as strict hand hygiene measures, using well-fitting face masks, and limiting eating or drinking during flights [6].

The most commonly used methods for SARS-CoV-2 diagnosis are polymerase chain reaction (PCR) and antigen tests [7]. The WHO diagnosis reference standard is by reverse-transcriptase PCR (RT-PCR) using nucleic acid amplification tests (NAATs) extracted from nasopharyngeal or oropharyngeal swabs [8]. However, PCR testing requires trained healthcare workers, and the laboratory time can take several days [9]. In comparison, rapid tests are often simpler to perform and the results are mostly available in less than 30 min [10,11]. However, rapid tests have relatively high false-negatives, and therefore are not used as reference standards to PCR tests in terms of sensitivity [10,11]. The third type of test is antibody testing but the process requires a sample of blood, and therefore it is mainly used to assess past infections [12,13].

Saliva specimens are highly stable and are used to test influenza A, influenza B, respiratory syncytial virus, and human bocavirus HboV-1 infections by PCR-based assays [14–17]. The U.S. Food and Drug Administration (FDA) recently granted emergency approval for saliva-based tests as an alternative to nasopharyngeal or oropharyngeal swabs to improve testing capacity for COVID-19 [18]. Saliva specimens can be self-administered by deep throat method, passive drooled, or buccal swab and stored in saliva collection kits [19]. Pair comparisons of nasopharyngeal swabs and saliva specimens have demonstrated good sensitivity for COVID-19 diagnosis [19]. In a study involving 214 adult in-patients, To et al. found saliva had high specificity (100%) and sensitivity (90.8%), but extraction of pure saliva from symptomatic patients may be limited should the saliva be highly viscous [14,20]. A meta-analysis by Butler-Laporte et al. [21] suggested comparable accuracy of saliva NAAT (pooled sensitivity of 83.2% and specificity 99.2%) to nasopharyngeal swab NAAT (pooled sensitivity 84.8% and specificity of 98%). Another meta-analysis by Nasiri [22] showed insignificant difference between nasopharyngeal swab and saliva specimens for COVID-19 disease diagnosis.

Some countries have selectively lifted travel restrictions imposed during the early phase of the COVID-19 pandemic with the conditional requirement for traveler health screening and infection control measures following recommendations management of Points of Entry (PoE) [23]. Currently, major airports implement COVID-19 screening but on arrival nasopharyngeal or oropharyngeal swabs can be both uncomfortable and pose additional transmission risks should the procedure induce coughing or sneezing at busy airport terminals. Saliva has the potential to be a non-invasive substitute specimen for SARS-CoV-2 diagnosis as nasopharyngeal swabbing is impractical for very scale mass screening. To explore further this potential, we used two different saliva collection methods and a laboratory processing time within 4 h of collection as a standard to determine diagnostic accuracy with paired nasopharyngeal swabs for COVID-19 screening among returning air travelers.

2. Materials and methods

2.1. Study design and participants

A total of 96 adult subjects (81 travelers and 15 non-travelers) with nasopharyngeal swabs RT-PCR confirmed COVID-19 infections were recruited prospectively from the day of admission at Sungai Buloh Hospital, a dedicated COVID-19 hospital in Malaysia from July to October 2020. All subjects have consented.

Subjects were instructed not to gargle, brush teeth, or chew gum 30 min before early morning saliva collection. Then, each subject was asked to pool saliva in their mouth for two to 3 min and then passively drool about 2 mls of saliva into a sterile plastic container and GeneFiX™ saliva collection kit separately. Next, a paired nasopharyngeal swab was taken as per standard protocol and the swab was placed in 3 mls of viral transport media (Fig. 1). All specimens were labelled, triple packaged, and placed in ice-pack containers for laboratory transfer within 4 h of collection.

2.2. Test methods

Laboratory testing was performed at Gribbles Pathology Malaysia blinded to the recruited subjects prior PCR results to avoid bias. Multiple Real-time PCR with the Alplex™ 2019-nCoV Assay (100T) was used for the detection of RNA-dependent RNA polymerase (RdRp), envelope (E), and nucleocapsid (N) genes [24]. RNA extraction for all specimen types was performed by using the NIMBUS automated specimen processing system. The input specimen volume was 300 μL while the elution volume was ~100 μL. The RT-PCR assay was performed according to the manufacturer’s instructions using 8 μL of the extracted specimen. The primer and probe sequences were used according to the manufacturer insert. The primer and probe sequences were performed in a total reaction volume of 25 μL, containing 8 μL of RNA, 12 μL of PCR reaction mixture and 5 μL of primer and probe mixtures. Thermal cycling conditions included 50 °C for 20 min for reverse transcription, inactivation of the reverse transcriptase at 95 °C for 10 min, 45 cycles of PCR amplification at 94 °C for 15 s and 58 °C for 30 s in the CFX96 detection system (BIORAD Sdn. Bhd.). For each run, viral template-positive controls and no-template controls were included.

Four classifications for the genes namely detected (positive 2019-nCoV), not detected (negative 2019-nCoV), presumptive positive, or invalid were reported. However, the interpretation took into account the different test results when more than one run or test per specimen for unconfirmed cases. For all three genes, the cycle threshold (Ct.) value cut-off point was 40. Any gene that reported a Ct. value of below 40 was defined as positive detection [24].

2.3. Analysis

For the population under study, demographic data including age, sex, ethnicity, days of illness, comorbidities, and category of the severity of illness were collected. The laboratory data were differentiated by the
3. Results

3.1. Participants

All subjects were recruited within a mean of 3-22 days (SD = 1-60) of being confirmed positive with RT-PCR assay. At the time of testing, 75%-0% of the subjects were asymptomatic or presymptomatic. The majority were male (68.8%), with a mean age of 34-26 years (SD = 12.9), absence of comorbidities (72.9%), and of Malay ethnicity (49.0%). Among the travelers, 77 were confirmed RT-PCR at the time of hospitalization whilst three travelers had close positive contacts. In this group, 11%-5% and 31% were classified as having mild illness and moderate illness respectively (Table 1).

3.2. Test results

In this group, the detection rate for SARS-CoV-2 with nasopharyngeal swabs, whole saliva, and GeneFix™ were similar (89.3%, 50.56; 87.8%, 43.49; 89.6%, 43.48). The difference between the two specimen types for RT-PCR tests was not statistically significant (Table 2). Our study shows comparable results for the genes tested in both whole saliva collected into the plain container and the GeneFix™ collection kits. The N2 gene was most frequently detected whilst the E gene demonstrated the highest viral load (mean = 2796 to 3010, SD = 314 to 385) (Fig. 2). As for non-travelers, lower Ct. values were detected in whole saliva as compared to GeneFix™ saliva specimens. The results showed that saliva specimens had high sensitivity (80.4%) and specificity (90.0%). The positive predictive value for the diagnosis of SARS-CoV-2 in our study was 91.8%. There was good agreement between both saliva collection methods with Kappa of 0.69 (Fig. 3 and Table 3). Fig. 4 plotted for Receiver Operating Characteristic (ROC) Curve for the saliva specimens against nasopharyngeal swabs showed a high level of agreement with reported area under curve (AUC) of 0.85.

4. Discussion

Saliva has diagnostic potential as it is rich in hormones, antibodies, and microbes that enters through blood via active carriage, passive diffusion, and ultrafiltration [25]. The source of oral biological fluids for SARS-CoV-2 diagnosis include oral specimens from upper respiratory tracts, gingival crevicular fluid, and saliva from infected salivary glands [26]. As most of our study subjects were asymptomatic or presymptomatic, we could not disregard the possibility that SARS-CoV-2 detected in saliva originated from salivary glands rather than the respiratory tracts [26].

The travel histories and positive RT-PCR results were consistent with the incubation period of SARS-CoV-2 of about 5–6 days [1]. This infectious state may extend beyond a week before an individual becomes clinically symptomatic [1]. Three of our study subjects shared meals with another fellow traveler who was later confirmed COVID-19 positive. Subsequently, all three were tested positives as well.

Currently, the optimal specimen type for detecting SARS-CoV-2 is nasopharyngeal swab [8]. The collection of nasopharyngeal swab may induce coughing and sneezing due to procedural irritation [9]. This predisposes to the spread of SARS-CoV-2 through aerosolization. We instructed our subjects to pool saliva and then passively drool into collection kits. This method is less invasive and is preferred over deep throat saliva or buccal swab as it can be self-administered [17]. The overall performance of saliva specimens was equivalent to nasopharyngeal swab for SARS-CoV-2 detection by RT-PCR [14,19]. These findings were consistent with the meta-analysis reported by Butler-Laporte [21], in which the diagnostic sensitivity of NAAT saliva of 83.2% (95% CI 74.7–91.4%) as compared to nasopharyngeal swab, 84.8% (95% CI 76.8–92.4%). Similar to the meta-analysis by Nasiri

### Table 1

| Characteristics and presentations of subjects (N = 96). |
|--------------------------------------------------------|
|                                                        |
| Age                                                   | 34 (28) (12.9) |
| Sex                                                    |                |
| Male                                                  | 66 (66.8) |
| Female                                                 | 30 (31.2) |
| Ethnicity                                              |                |
| Malaysian                                              | 47 (49.0) |
| Malay                                                  | 17 (17.7) |
| Chinese                                                | 4 (4.2) |
| Indian                                                 | 6 (6.2) |
| Others                                                 | 22 (22.9) |
| Day-to-recruitment (days)                              | 3.22 (1.60) |
| Day of illness (days)                                  | 2.00 (3.13) |
| Co-morbidities                                         |                |
| Yes                                                    | 26 (27.1) |
| No                                                     | 70 (72.9) |
| NIH severity of illness classification                |                |
| Asymptomatic or presymptomatic                         | 72 (75.0) |
| Mild illness                                           | 11 (11.5) |
| Moderate illness                                       | 3 (3.1) |
| Severe illness                                         | 0 |
| Critical                                              | 0 |
| Unclassified                                          | 10 (10.4) |
| Risk factors                                           |                |
| Travel history                                         | 81 (84.4) |
| No travel history                                      | 15 (15.6) |

SD= Standard Deviation.

* The distribution is normally distributed.

* Day of illness for asymptomatic patients is counted from the day of swab is positive.

* Three travelers also had history of positive contact.

* Negative RT-PCR controls.
our study showed no significant differences between the specimens, thus suggesting saliva is preferable for ease of collection and by patients themselves. About one-fifth of subjects were tested negative for both saliva specimens, but paired nasopharyngeal swabs taken at the same setting were found to be positive. The respective Ct. values for all these subjects were above the cut-off point of 40, hence considered SARS-CoV-2 as undetectable [24]. Centers for Disease Control and Prevention (CDC) have reported increasing epidemiologic studies showing positive COVID-19 infections documented by positive viral cultures amongst asymptomatic or presymptomatic patients and could mean transmit during the presymptomatic incubation periods [27]. However, the proportion of disease transmission of asymptomatic or presymptomatic cases compared to symptomatic cases was unclear [27]. Thus, the asymptomatic or presymptomatic nature of the disease poses major challenges for the containment of COVID-19 as not all individuals are being tested unless having contact risks [1,4,27].

Self-collected saliva by returning travelers is advantageous as it reduces the need for personal protective equipment, trained personnel, and specialised equipment for specimen collection. Travelers could self-provide the saliva specimens and proceed with home-quarantine while waiting for the test results. By substituting nasopharyngeal swab with saliva, it can reduce the risk of aerosolization and transmission of infections to healthcare workers. Our study showed comparable results for the genes tested in both whole saliva collected into plain containers and into GeneFiX™ kits. Other studies similarly concluded that saliva specimens are highly stable for PCR-based assays without the need for a universal transport medium [14–17]. A plain container for saliva collection should suffice for practically, provided the processing time occurs within 4 h. However, if laboratory processing time is likely to be delayed, it is preferable to use universal transport media for collected saliva.

Among our study subjects, 15 were admitted based on the history of positive close contacts. In this group, most of the genes detected demonstrated lower mean Ct. values consistent with the early stage of the disease. High viral loads detected corresponded to the early identification of the subjects leading to specimen collections at an earlier phase of illness than travelers. Thus, saliva specimens are highly applicable for the diagnosis of SARS-CoV-2 for those with positive contact histories. Our study also found out that N2 gene based test kits are sufficient for diagnosis of SARS-CoV-2.

Optimisation of pure saliva specimens is critical for accurate laboratory testing. Oral microorganisms are dependent on the saliva pH and thrive better in acidic conditions. Thus, using mouth gargle before saliva specimen collection may affect saliva pH and render the saliva specimen less sensitive [28]. We instructed all of our subjects to avoid gargling with any form of solution, chewing, or even brushing teeth 30 min before saliva collection. The timing from saliva collection to processing plays a vital role in the viability of the specimen in order to minimize the chance of viral degradation. We minimized the potential of
transportation error in our study by ensuring all specimens were ice-packed and our time-of-collection to processing at the laboratory were within 4 h, consistent with published literature [29–32].

Some countries including Malaysia have eased travel restrictions but there are barriers to re-open the aviation industry fully as all governments are anxious about COVID-19 transmissions via air travel [23,30]. The current air travel capacity depends on unrestricted mobility of COVID-19 negative tested travelers [5]. The risks of transmissions can

![Fig. 3. Concordance of saliva specimens among travelers.](image)

**Table 3**

Level of agreement between saliva specimens and nasopharyngeal swab specimens.

| Specimen Type | Nasopharyngeal swab (N = 96) | Kappa value | p-value | Positive Predictive Value (%) | Negative Predictive Value (%) |
|---------------|-------------------------------|-------------|---------|-------------------------------|-----------------------------|
| Whole Saliva  | Detected                      | 0.69        | <0.0001 | 91.8                          | 76.6                        |
|               | Not detected                  |             |         |                               |                             |
| GeneFiX™ saliva | Detected                      | 0.67        | <0.0001 | 91.7                          | 75.0                        |
|               | Not detected                  |             |         |                               |                             |

*a* Chi-Square test for independence.

![Fig. 4. Receiver Operating Characteristic (ROC) curve for saliva specimens vs. nasopharyngeal swab specimens.](image)
be mitigated by new methods of easy screening and testing for SARS-CoV-2. Our study showed that fresh drooled saliva is a reliable specimen with a high concordance rate to nasopharyngeal swab.

5. Conclusion

Saliva for SARS-CoV-2 screening is a simple accurate technique comparable with nasopharyngeal swab RT-PCR. This can complement the current testing method by using RT-PCR among travelers.

Ethical approval

Ethical approval was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (Ref: KKM/NIHSEC/P20-1186(12)).

Conflicts of interest

The team members declare no conflicting interests in conducting the study.

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Author statement

Investigation and Project Administration were performed by AAMT, KMP, PXK, DKFY, MAMA, ANS, MAY, MAMP, AHH and SKC. Laboratory Processing was conducted by NN, CC, GR, MG, SS, HKLS and AA. Formal analysis by PXK and CC. All authors contributed to the reviewing and approved the final version.

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