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SPECIAL ARTICLE COVID-19

Proposal of Research Model for the Detection of COVID-19 among Asymptomatic Carriers

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Abstract

Coronavirus disease 2019 (COVID-19) is a pandemic and rapidly progressing infectious disease that represents a global health care emergency due to severe acute respiratory syndrome. Rapid tests detect antigen or antibody presence, which is useful for patient care and for assisting in disease surveillance and epidemiological research. The complicating aspect of the COVID-19 spread may be due to asymptomatic individuals. Unfortunately, asymptomatic individuals are not detected in the early stages of infection, which could help to prevent community spread. The present paper shares an opinion through the proposal of a research model for detecting COVID-19 among asymptomatic carriers.

Keywords
- COVID-19
- asymptomatic
- PCR
- diagnosis
- epidemiology
- saliva

Introduction

The pandemic of coronavirus disease 2019 (COVID-19) is a global health emergency concern due to severe acute respiratory syndrome (SARS) caused by the novel coronavirus (nCoV). Severe acute respiratory syndrome-related nCoV is most probably originated from Chinese horseshoe bats (*Rhinolophus sinicus*), and pangolins are most likely the intermediate host. The spread of the COVID-19 infection initially originated from animal to human transmission, which was followed by sustained human to human spread.[1] The average estimated incubation period of COVID-19 is approximately 5 to 6 days; however, evidence reported that symptoms may appear around 14 days. Hence, medical and epidemiological observation recommend 14 days of quarantine for the identification of exposed individuals.[2] The most common early symptoms of COVID-19 are dry cough and fever, and some patients reported breathing difficulty and fatigue. The diagnosis of COVID-19 is established based on clinical, epidemiological, and laboratory reports. The epidemiological information, such as history of travel, import-related or resident of affected region is also important for tracing the route of transmission. In routine practice, specimen for laboratory diagnosis is obtained from the mucosal secretion of respiratory tract through nasal swabs. The laboratory diagnosis is done by rapid test, which either detects the presence of viral proteins expressed by COVID-19 or antibodies in the blood of individuals with COVID-19 infection. However, the World Health Organization (WHO) does not recommend the use of antigen- or antibody-detecting rapid diagnostic tests for patient care but encourages its use for epidemiological and surveillance research. The WHO stated that in-vitro diagnostic tests such as real-time polymerase chain reaction (RT-PCR) and cobas SARS-CoV2 (Roche Diagnostics Corporation, Indianapolis, IN, USA) are quality-assured tests for the detection of COVID-19. However, it is important to mention that a negative RT-PCR test result from a suspected patient does not exclude infection, and the patient should be cautiously watched for any relevant clinical symptoms of COVID-19.[3]

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Evidence for Transmission of nCoV from Asymptomatic Individuals

A rapid and accurate detection of COVID-19 is crucial in controlling the outbreak in the community, and a model for the identification of asymptomatic COVID-19 patients is essential because these patients increase the COVID-19 burden. Studies identified that angiotensin-converting enzyme 2 (ACE2) is the functional receptor of COVID-19 infection and plays a significant role in SARS lung pathogenesis. The expression of ACE2 was identified in the respiratory tract through immunohistochemical analysis. Similarly, the expression of ACE2 was detected in the immunohistochemical method in minor salivary glands and, more specifically, in epithelial cells lining salivary gland ducts. A study mentioned that the epithelial cells lining of the salivary gland ducts are early targets of the nCoV, and ductal cells get infected eventually producing infected saliva.[4] Thus, it can be mentioned that salivary glands appear to be potential targets for the nCoV in addition to the respiratory tract. This also indicates that early detection of the nCoV may be possible before lung lesions appear. Hence, the salivary gland can serve as a major source of virus in the saliva, which may be a source of transmission to others by asymptomatic individuals. To et al stated that detection of nCoV from salivary samples may reach 91.7%, and salivary samples can also cultivate live nCoV, thus providing an evidence that transmission of nCoV from asymptomatic individuals may be originating from the infected saliva.[5,6]

Proposal of Research Model for the Detection of nCoV in Asymptomatic Carriers

Nasal swab tests are frequently employed in the testing for detection of nCoV. Although nasal swab remains the gold standard specimen of choice for most patients with respiratory infections, salivary specimens are reported for assisting in detection of nCoV infection.[7] Eight published papers of salivary-related research in nCoV infection were observed in the PubMed database. (https://pubmed.ncbi.nlm.nih.gov/?term=-Saliva%20and%20nCoV&pos=6) Five of them were original research studies, and the findings of those papers were outlined in ►**Table 1**.[4,5,8–10] The proposal of salivary testing is not to replace nasal swab test, but to identify the validity of salivary testing among asymptomatic patients. Salivary samples are collected by instructing patients to expectorate saliva (0.5–1 ml) into a sterile container. Two ml of viral transport media (VTM) should be added immediately to the salivary sample and submitted for molecular analysis.

Although the studies listed in ►**Table 1** outline the consistency of salivary detection of COVID-19, none of the existing studies employed both nasal swab and salivary methods of analysis on either symptomatic/asymptomatic COVID-19 patients. The present paper shares an opinion through a research model for identifying and understanding asymptomatic carriers through a comparative analysis. It would be easier to understand the efficacy of salivary detection through molecular diagnosis when both nasal and salivary samples are employed on symptomatic and/or asymptomatic patients. (►**Figure 1**) The data obtained from such research will allow us to compare the results between nasal and salivary samples and assist in arriving a conclusion on efficacy of salivary approach. The goal of this research model is to identify the asymptomatic patients through salivary-based molecular diagnosis. Reliable salivary-based detection of asymptomatic carriers will provide a guidance in quarantining with the aim to prevent community spread through asymptomatic carriers.

Considering the available evidence that states COVID-19 may be transmitted by asymptomatic individuals who may

Table 1 Studies that employed salivary samples for molecular detection of novel corona virus

No.	Study hypothesis	Study findings/ conclusion	Author and year of publication
1	Salivary testing from suspected COVID-19 patients based on clinical and epidemiological criteria.	nCoV was detected in the self-collected saliva of 91.7% of patients.	To et al 2020[5]
2	Ferret model of SARS-COV-2 study employed to understand the infection and transmission that recapitulates aspects of human disease.	SARS COV-2 infected ferrets showed the presence of the virus in nasal washes and saliva up to 8 days postinfection.	Kim et al 2020[8]
3	Analysis of COVID-19 from salivary samples of patients with known clinical and laboratory data. Samples were collected from patients with severe to very severe COVID-19 symptoms.	All the samples tested positive for nCoV. Interestingly, two patients showed positive salivary results while nasal swabs were negative.	Azzi et al 2020[9]
4	Prediction of intrinsic disorder in MERS-CoV/HCoV-EMC supports a high oral-fecal transmission.	Oral-saliva and oral-urine routes are also a possibility for viral transmission.	Goh et al 2013[10]
5	Viral replication in the upper respiratory tract may contribute to the rapid viral shedding into saliva droplets.	Demonstrated for the first time in the literature that the ACE2 epithelial cells of the salivary gland ducts are early targets of SARS-CoV infection. The findings provide evidence that salivary gland epithelial cells can be infected in vivo soon after infection, thus providing source of virus in saliva, particularly in early infection.	Liu et al 2011[4]

Abbreviations: ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; HCoV-EMC, Human Corona Virus-Eramus Medical Center; MERS-CoV, Middle East respiratory syndrome-coronavirus, nCoV, novel coronavirus; SARS-CoV, severe acute respiratory syndrome-coronavirus.

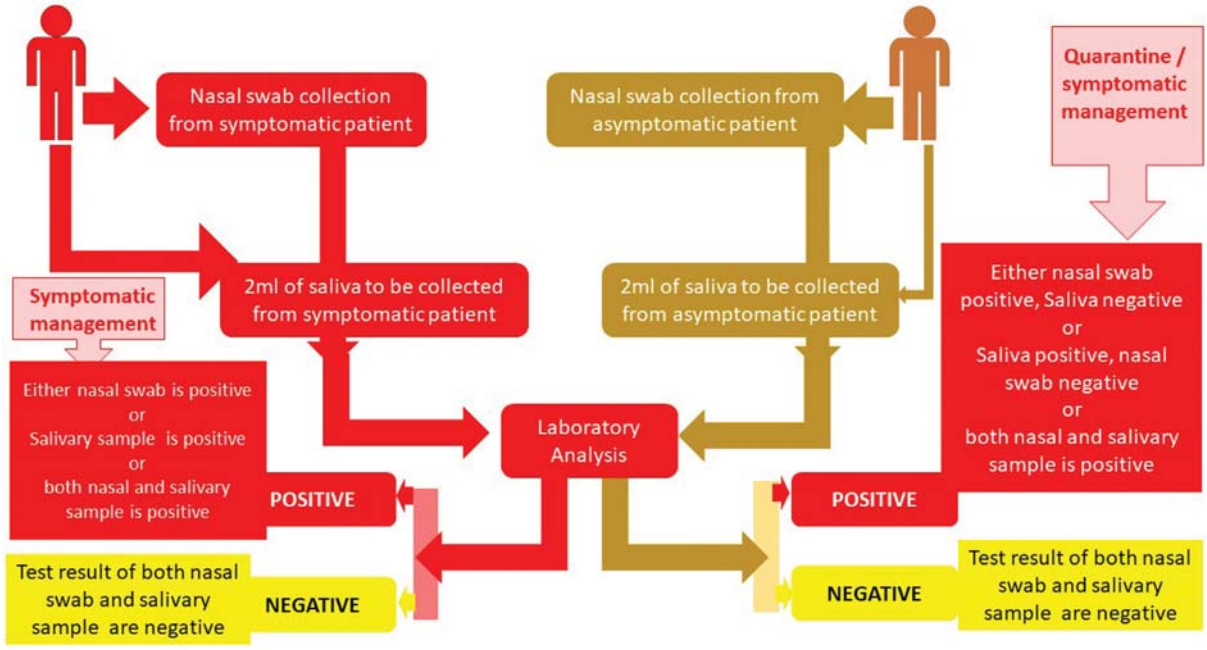

Fig. 1 Research model for comparative analysis of nasal and salivary specimens for molecular detection of nCoV in both symptomatic and asymptomatic individuals.

have an infected saliva. It is well understood that conducting a research study to employ both nasal and salivary samples on patients with suspected COVID-19 infection is resource dependent, for instance, on funding, time, and availability of adequate patients and laboratory support. The countries that could afford the cost for processing laboratory specimens should be encouraged in conducting the research to validate the salivary analysis among asymptomatic individuals. Thus, the proposed research model is aimed at identifying asymptomatic carriers and, by extension, to create a scope for policy-making decisions on preventing community spread through asymptomatic carriers.

Conflict of Interests

The authors declare that there is no conflict of interests.

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