Editorial

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Saliva serological testing could be alternative rapid pre-surgical operative screening tests to nasopharyngeal swab testing in diagnosis of COVID-19

Keywords: nasopharyngeal swab, saliva, IgM, COVID-19, RT-PCR, NPS

Abbreviations: RT-PCR, reverse-transcriptase-polymerase-chain reaction; IgM, immunoglobulin M; RNA, ribonucleic acid; RBD, receptor-binding domain; NPS, nasopharyngeal swab; ICU, intensive-care-unit; qRT-PCR, quantitative reverse-transcriptase-polymerase-chain reaction

Volume 9 Issue 2 - 2021

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Received: March 13, 2021 | **Published:** April 01, 2021

Editorial

Characteristically, after infection, antibodies are detected in the blood of individuals, particularly individuals with few or mild symptoms. In patients with varying symptoms of COVID-19 and negative results of reverse-transcriptase-polymerase-chain reaction (RT-PCR) tests, the testing has a significantly clinical role when nasopharyngeal swabs are taken more than 5 days after symptom onset.[1,2] Immunoglobulin M (IgM) rises soonest, whereas IgA and IgG persist. IgG alone. The maximum sensitivity for IgM alone, IgA alone, and IgG alone appear during the days 15-21 after the symptom onset that are 75.4 % (64.3-83.8), 98.7 % (39.0-100), and 88.2 % (83.5-91.8), respectively,[3] whereas the specificity at all times for IgM alone and IgG alone are 98.7 % (97.4-99.3) and 99.1 % (98.3-99.6), respectively.[3] The sensitivity and specificity of the antibody tests are critical due to false negative rates of RT-PCR that are between 2 % and 29 %.[3] A previous study on immunological assessment of SARS-CoV-2 (COVID-19) infections in China revealed that 81.1 % (30/37) and 62.2 % (23/37) of asymptomatic individuals tested positive for IgG and IgM, respectively and 83.8 % (31/37) and 78.4 % (29/37) of the symptomatic patients tested positive for IgG (around 3-4 weeks after COVID-19 exposure) and IgM, respectively.[4] In acute phase that the viral ribonucleic acid (RNA) can be identified in a respiratory sample, IgG levels in symptomatic patients were significantly statistical higher than those in the asymptomatic individuals.[4]

The pre-test probability of infection has much influence on the interpretation of the serological test results not only influenced by the accuracy of the test itself. When screening suggestive symptomatic individuals, the pre-test probability will be much higher, compared to asymptomatic persons.[5] COVID-19 screening is essentially amounted by non-specific indication and population-based policies on testing. In consequences of testing with uncareful consideration, this risks the potential harm. In more affluent populations, the rates of testing will be higher[6] that limits the estimates of seroprevalence. The Royal College of Pathologists (RCPath) developed seven principles for production of a COVID-19 testing strategy. Testing being carried out for a purpose is one of these RCPath's principles.[7] Nevertheless, denial of requesting SARS-CoV-2 (COVID-19) antibody tests for reassurance should be cautioned.[8,9] In eliminating COVID-19, a combination of B and T cell immunity is likely to involve for production of protective-immunity memory.[5] Nevertheless, currently, several longitudinal studies demonstrated waning of antibody levels.[10] With a lower antibody levels, whether the protective immunity will be sustained is questionable.[5] A recent study revealed that produced antibodies can provide long-term immunity, whereas non-neutralizing antibodies can be generated. Antibody enhancement, a phenomenon that can facilitate a more severe-secondary infection.[11] This phenomenon is not to date with SARS-CoV-2 (COVID-19), but it has been demonstrated in other coronaviruses.[11]

Several immune-based assays were developed against different SARS-CoV-2 (COVID-19) viral proteins as the followings:

- Entire Spike (S) protein, IgG antibody from patient serum can cross-react with SARS-CoV and MERS-CoV[12]
- S1 subunit of Spike (S) protein, IgA, IgG antibodies from patient serum can cross-react with SARS-CoV only,[12]
- Receptor-binding domain (RBD), IgG antibody from patient serum can cross-react with SARS-CoV only[12]
- Nucleocapsid (N), IgG antibody from patient serum can cross-react with SARS-CoV only.[12]

IgG antibody responses sustained for at least 34 months after outbreak in persons with laboratory-confirmed MERS-CoV infection,[13] whereas IgG levels in SARS-CoV-infected individuals were sustained for more than two years.[14,15] Neutralizing antibodies that associate with the numbers of virus-specific T cells have been detected in most COVID-19 convalescent patients.[16–19] Long et al.,[4] demonstrated in their study that IgG antibody and neutralizing antibody levels initiate decreasing within 2-3 months after infection in the majority of persons with recovery from SARS-CoV-2 (COVID-19) infection.[4] Nevertheless, an analytical study of the dynamics of neutralizing antibody titers demonstrated reduced neutralizing antibodies around 6-7 weeks after illness onset.[20]

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Saliva samples[21–23] and dried blood spots[24,25] have been used successfully for detecting antibodies against several infectious diseases although serum is the typical sample type. Saliva sampling allows potential self-collection and substantial scale of testing. IgG antibody titer for Hepatitis B correlates well between saliva and plasma.[23] A recent study conducted by Randal and colleagues using multiplex SARS-CoV-2 antibody immunoassay-based on Luminex technology for testing 167 saliva and 324 serum samples, including 134 and 118 negative saliva and serum samples, respectively, collected before the COVID-19 pandemic, and 33 saliva and 206 serum samples from patients with RT-PCR-confirmed SARS-CoV-2 (COVID-19) infection demonstrated that matched saliva and serum SARS-CoV-2 (COVID-19) antigen-specific IgG responses were statistically correlated.[26] The saliva anti-nucleocapsid (N) protein IgG response resulted in the highest sensitivity (100 % sensitivity at least 10 days post-SARS-CoV-2 (COVID-19) illness onset), whereas the saliva anti-RBD IgG response resulted in 100 % of specificity.[26] The temporal kinetics of IgG, IgA, and IgM in saliva of RT-PCR-confirmed-SARS-CoV-2 (COVID-19)-infected patients were consistent with those demonstrated in serum.[26] A recent meta-analysis of the sensitivity of the COVID-19 (SARS-CoV-2 viral RNA) diagnostic testing in saliva specimens in comparison to the sensitivity of the nasopharyngeal swab (NPS) tests demonstrated that the sensitivity for saliva tests was 91 % (CI=80-99 %), whereas the sensitivity of the NPS tests was 98 % (CI=89-100 %).[27] Saliva could be an alternative valid strategy to serum for detecting antibodies against SARS-CoV-2 (COVID-19).

In conclusion, the effective antibody-mediated immunity is not enough evidence to guarantee the protective mechanism against re-infected-COVID-19. The type of specimen collection and technical errors, the methods used before patient discharging, and the presence of fecal viral RNA without evidence of viral replication in fecal swab should be considered. Viral culture, inflammatory target monitoring, genomic comparison of SARS-CoV-2 (COVID-19) strains involving both episodes of infection (at least one episode of the laboratory test during a 14-day post-hospital discharge period of quarantine period for patients with COVID-19), and evaluation of innate and adaptive immunity are recommended for understanding of the recurrences of COVID-19. Further urgent studies should be identification of the parameters associated between the viral load and clinical parameters, such as certain comorbidities, symptom severity, hospital admission and direct hospital discharge, hospital length of stay, intensive-care-unit (ICU) admission, length of need for oxygen support, and overall survival. Further exploration quantitative VLs from lower respiratory tract tissue and blood in severe COVID-19 patients may prove to be a better predictor for clinical outcomes. Future studies will address SARS-CoV-2 (COVID-19) VL dynamics and the quantitative association with neutralizing antibodies, cytokines, pre-existing conditions, and therapies. Serological data greatly supplement the laboratory results from the quantitative reverse-transcriptase-polymerase-chain reaction (qRT-PCR), the design of virus elimination programs (seroepidemiology), discovery of the monoclonal antibodies, and development of SARS-CoV-2 (COVID-19) vaccines, particularly the saliva tests could offer a promising alternative test to the NPS tests for the COVID-19 diagnosis.

Funding

None.

Acknowledgments

None.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Citation: Cheepsattayakorn A, Cheepsattayakorn R, Siriwanarangsun P. Saliva serological testing could be alternative rapid pre-surgical operative screening tests to nasopharyngeal swab testing in diagnosis of COVID-19. *MOJ Surg.* 2021;9(2):49–51. DOI: 10.15406/mojs.2021.09.00191