Pitfalls in the Diagnosis or Screening of COVID-19 Cases Based on Antibody Detection: Review and Solution

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REVIEW ARTICLE

Pitfalls in the Diagnosis or Screening of COVID-19 Cases Based on Antibody Detection: Review and Solution

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ABSTRACT

SARS-CoV-2 was found in Wuhan, China and has become a global pandemic until now. To achieve control of COVID-19, we need accurate and rapid diagnostic tests. There are two kinds of diagnostic: molecular tests to detect viral RNA and serological tests to detect anti-SARSCoV-2 immunoglobulins. Serological tests become an alternative or a complement to RT-PCR as it might be cheaper and easier. Combining IgM and IgG detection resulted in higher sensitivity than detecting either isotype alone. However, the tests have some limitations to measure IgM or IgG antibodies. Therefore, using merely such tests to diagnose COVID-19 will miss any infections. Consequently, the diagnosis or screening for COVID-19 using antibody test needs to be evaluated. We aim to decrease the risk of false-negative or false-positive in the tests.

Keywords: Diagnosis, Screening, COVID-19, Antibody detection, Molecular testing

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INTRODUCTION

In December 2019, a novel RNA coronavirus was found in Hubei Province, China. It causes acute respiratory distress syndrome (ARDS) and rapid multi-organ failure (1). Coronaviruses are viruses containing a single strand of positive-sense RNA (2). Spike protein is one of the main antigen proteins and structure in viral. It made of a highly glycosylated protein. The envelope, membrane, and nucleocapsid proteins are other structural proteins (3). Most of the patients experience difficulty to breathe in one week and the severely ill patients soon develop ARDS and other inflammations (4). SARS-CoV-2 is transmitted from human to human through droplets (5).

SARS-CoV-2 particles are responsible for virus entry and inducing the innate and adaptive immune response. Host of ACE-2 protein will be bound by viral spike1 (S1) protein. Then, the virus particles will carry out to endocytosis process. SsRNA viral will be detected by the immune system through TLR7 and TLR8 and transcription factor will active in NF-κB and MAPK pathways to induce the expression of pro-inflammatory cytokines in host. ssRNA and dsRNA virus generated a intermediate in virus replication, and it will be recognized by RIG-I and MDA5 which further induce the expression of type I IFN that leads to antiviral state (5). Major histo compatibility complex (MHC) class I will present viral peptides to CD8 + cytotoxic T cells. CD8+ cytotoxic T cells will become active and begin to divide and show clonal expansion and develop virus-specific effectors and memory T cells. Infected tissue cells will be lysed by CD8 + T cells. All viruses and their particles will be recognized by APC and then it will be presented to CD4 + T cells via MHC class II. B cells themselves can be directly recognize the virus and it will automatically activate. B cells can also make interaction with CD4 + T cells. B cells develop into plasma cells and increase the production of specific antibodies for viruses with IgM, IgA and IgG types (6).

In the early 1st week of symptom onset, IgM and IgA were detected, while IgG was detected at around 14 days after the initiation of symptoms (7). One of the tests to diagnose COVID-19 is serological antibody detection, and this test detects IgM, IgG, or total antibodies (typically in the blood) against SARS-CoV-2. There are many methods for serological antibody detection including ELISA, LFIA, and

chemiluminescent immunoassay (8). Nevertheless, the LFA, CLIA and ELISA were limited in sensitivity and specificity (9). In some of the tests, false-positive and false-negative results were still found (10). Failure to detect people with COVID-19 can cause a delayed treatment and risk of further spreading infections to others (11). Therefore, in this article, the writer wants to discuss the evaluation for diagnosis or screening of COVID-19 cases based on antibody detection.

ANTIBODY PROFIL IN COVID-19

The production of IgA, IgM, and IgG antibodies was positive inearly times after the onset of symptoms. The IgM/IgA antibodies as well as the IgG antibodies can be detected from 5 to 14 days PSO, respectively. The IgA antibodies were at a higher positivity rate compared with the IgM antibodies. IgG levels were consistently higher than IgM levels which cause the IgG antibodies to be in the body for quite a long time and able to contribute to long-term immune memory against SARS-CoV-2 (12). Interestingly, Zhang et al. found that increasing of IgG response has a correlation to severity of disease. It can be a marker to differentiate between severe and non-severe cases. Another study also showed that the specificity was also excellent for IgG (100%), but the specificity was significantly different between IgA (78.9%) and IgM (95.8%) in 14 days after onset of symptoms (13). Combining both IgM and IgG SARS-CoV2 detection provides the basis of COVID-19 diagnosis and screening. For early diagnosis, we can use IgM and IgG to help monitor the COVID-19 status (14).

ANTIBODY TESTING OF COVID-19

Utility of antibody testing: i) to establish the diagnosis of patients with special conditions and experiencing some symptoms; ii) to track the transmission; iii) to know the potential for immune disease or other disease; and iv) for sero-epidemiological studies, to understand the spread of COVID-19 (15). The methods used for antibody detection are ELISA, CLIA, and LFIA. All methods are made to detect Immunoglobulin G and/or Immunoglobulin M antibodies (or sometimes in some cases to detect the total of antibodies) against S (mainly RBD) and/or N viral proteins of human sera/blood samples (16).

EVALUATION OF ANTIBODY TESTING

The results of a Taiwanese study about the ability of rapid test- IgM and IgG antibodies in 14 COVID-19 patients are sensitivity (78.6%) and specificity (100%), respectively (12). While based on Kontou et al, on (15) studies from LFIA tests, it has been shown that a combination of IgG and IgM is more sensitive than detecting one of the antibodies alone (15). Combination of Immunoglobulin G-Immunoglobulin M ICT cassette is suitable for the rapid screening of SARS-CoV-2 infection among positive COVID-19 patients, suspect patients and asymptomatic SARSCoV-2 carriers (17). Several LFIA tests have shown false-positive results there are several causes in false resulted like cross-reactivity of non-specific antibodies (e.g. have been exposed to other types of corona virus). We have to collect full information including the patients' hometown or native areas, ethnic groups, children, as well as those with immunology disease (18).

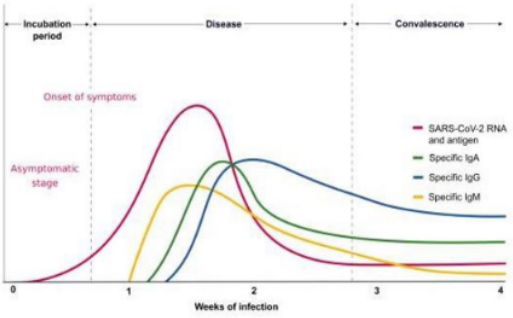

Figure 1 : The ELISA test showed that the detection of IgG, IgA, and IgA combined IgG has higher sensitivity and specificity at > 10 days after symptom onset.

Study result based on the ELISA test showed that the detection of IgG, IgA, and IgA combined, IgG has higher sensitivity and specificity at > 10 days after symptom onset. In addition, for CLIA method, the sensitivity was 65.5%, 88.8% and 100.0% when tested within 0-6 days, 713 days and 14 days after the onset of symptoms with great specificity (99.8%) (14).

The meta-analysis showed that ELISA and CLIA have high specificity. CLIA and ELISA have better sensitivity (90%–96%) and followed by LFIA and FIA (80% to 89%) (11). Based on the three methods, the specificity was high when tested on COVID-19 patients but not suspected.

Meanwhile, the specificity of LFIA and CLIA was lower when tested on positive patients with COVID-19. The Specificity of LFIA was lower when estimated in patients with other viral infections, while ELISAs or CLIAs is higher (19). False-positive and false-negative were still found in many tests. Cross-reaction with other types of coronaviruses can make antibody tests less specific and create false-positive results (16). Meanwhile, false-negative is caused by incorrect timing of diagnosis and low antibody because of inter-individual differences in the immune response (20).

PROPOSED SOLUTION

A serological diagnostic is useful to diagnose patients with acute respiratory distress syndrome and a negative PCR assay. Specimen collection is recommended in

the 2nd week of the disease. There are 2 things that must be understood for early diagnosis of COVID-19 based on the antibody detection: the window period for diagnosis must be shortened and a good specificity must be increased (21). Antibody sensitivity can be higher than the RNA test in 8-21 days after PSO. During acute and convalescent phase, understanding viral and host interactions is important to be able to know both the timing of early seroconversion after an exposure to SARS-CoV-2 and the following duration of antibodies (22). Some studies have shown that the use of S antigen is more sensitive than N antigen in ELISA tests. Because the S antigen has a higher sensitivity, earlier immune response to this antigen, more specifically, and cross-reactivity with less conserved regions of spike proteins existing in other coronaviruses is lower (16). The condition of the patients and the stage of the disease can be taken into consideration when collecting samples to support the accuracy of the diagnosis. Good quality of sampling when the initial day of illness or symptoms occur is the upper respiratory tract, while for the later stage, the use of sputum is more sensitive (23).

CONCLUSION

We found that sensitivities of LFIA method were lower compared with the ELISA and CLIA methods. CLIAs had a lower specificity among the three tests. The level of sensitivity and specificity of each test is different and it depends on commercial kits used. Cross reactivity between anti–SARS-CoV-2 with other types of coronaviruses can occur and be the cause of falsepositive results. Incorrect timing of diagnosis can lead to false-negative due to low antibody. Therefore, to avoid a missed diagnosis in people infected with SARS-CoV-2, we recommend using ELISA or CLIA instead of the widely used LFIA method.

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