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Clinical Utility of SARS-CoV-2 Antibody Testing

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Abstract

SARS-CoV-2 antibody assay is a test that checks whether an antibody against the SARS-CoV-2 virus has been formed in the blood after SARS-CoV-2 infection or vaccination. SARS-CoV-2 antibody is detected 1–2 weeks after infection, and antibodies are produced in more than 90% of infected patients. The duration for the formation of antibodies differs by individual and by type of antibody. In the case of IgG, it is at least several months or longer, and the relationship between antibodies and immunity is being studied. As test methods, enzyme-linked immunosorbent assay (ELISA), chemiluminescence immunoassay (CIA), immunochromatographic assay, and neutralizing antibody assay have been developed and used. The target antibody to be detected differs depending on the type of recombinant antigen and the type of secondary antibody in reagents. Many kinds of commercialized SARS-CoV-2 antibody assays are currently being developed, and the S (spike) protein, N (nucleocapsid) protein, S1 or RBD (receptor binding domain) part of the S protein, and a mixture of these antigens are used as recombinant antigens of reagents. IgG, IgM, IgA, or total immunoglobulin antibodies in patients' blood that react with these reagent antigens are detected. In this review, the types and performance of SARS-CoV-2 antibody tests and the guidelines for COVID-19 antibody tests published domestically and abroad were investigated.

Keywords

Antibody test
COVID-19
Guideline
SARS-CoV-2

1. Introduction

Coronavirus disease 2019 (COVID-19) refers to a respiratory syndrome caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is a novel infectious disease syndrome, a class 1 infectious disease (http://ncov.mohw.go.kr/). It began in Wuhan, China, in late 2019 and has spread rapidly around the world due to its highly contagious and infectious nature, resulting in 126,890,643 confirmed cases and 2,778,619 deaths (2.2% mortality

rate) globally as of 30 March 2021, and 102,141 confirmed cases and 1,726 deaths (1.7% mortality rate) in South Korea (https://covid19.who.int/) [1].

SARS-CoV-2 virus is a positive-sense single-stranded RNA virus belonging to the Coronaviridae family and is a spherical virus with a diameter of 80–200 nm [1-3]. It contains four structural proteins, the spike (S) protein, the nucleocapsid (N) protein, the membrane (M) protein, and the envelope (E) protein, with the S protein projecting outward to form a characteristic crown shape. Inside the envelope is a helical N gene containing RNA, and the genome is approximately 30,000 bp in size [2]. In this review, we investigated the current status of recently developed COVID-19 antibody tests to diagnose the global pandemic of COVID-19 since last year and their clinical utility among domestic and international COVID-19 antibody testing guidelines.

2. Types of COVID-19 antibody tests

Viral antibody tests detect the presence of antibodies to SARS-CoV-2 in a patient's serum, and kits are currently available to detect S- or N-protein-specific IgG antibodies, IgM antibodies, IgA antibodies, and neutralizing antibodies to SARS-CoV-2 [3-5]. Antibodies to coronavirus can be detected days after infection and can be detected for months or longer, which has the advantage of indicating recent or previous infection [6]. However, antibody tests should not be used alone to determine acute infection with COVID-19 but should be used as an adjunct to other diagnostic methods, such as polymerase chain reaction (PCR), because a single antibody test cannot distinguish between past and current infections, and may be produced more than one week after infection and miss early infection. It is generally accepted that antibody testing is diagnostically useful in viral diseases when antibodies change from negative to positive (seroconversion) in two or more blood draws 2–3 weeks apart in the same patient, or when there is a significant increase in antibody titers measured 2–3 weeks later, or when IgM antibodies are positive, indicating recent infection. However, since SARS-CoV-2 is a novel virus, test products have been recently developed and the sensitivity and specificity of each diagnostic product may vary depending on the antigen used in the reagent, the performance of these products has not been fully validated, and the characteristics of the antibody, such as the positivity rate in individual populations, the duration of the antibody, and the correlation with immunity, have not yet been fully clarified, so further research and data should be accumulated. In addition, if the prevalence rate is low, such as in Korea, the probability of false positives is high even if the test is positive, so when interpreting individual results, the probability of false positives and false negatives depending on the prevalence rate should be kept in mind.

Currently, coronavirus antibody tests can be roughly divided into those that detect binding antibodies and those that detect neutralizing antibodies. For detecting binding antibodies, various commercialized test reagents have been developed using the principles of enzyme-linked immunosorbent assay (ELISA), chemiluminescence immunoassay (CIA), and immunochromatographic assay. Compared to rapid immunochromatographic assays, ELISA and CIA methods have the advantages of higher assay sensitivity and the use of 96-well plates, which are convenient for testing a large number of samples simultaneously. Rapid immunochromatography has the disadvantage that its sensitivity is somewhat lower than ELISA and CIA, but it has the advantage that there is no loss of reagents when testing one sample at a time, and results can be obtained within 15–30 minutes with simple operation without special equipment. Tests to detect neutralizing antibodies are tests to determine whether a patient's serum contains antibodies that can neutralize the virus [6], such as the traditional plaque-reduction neutralization test (PRNT) or microneutralization test, and virus neutralization tests (VNT) to determine whether the SARS-CoV-2 virus can be used to inhibit viral proliferation, pseudovirus

neutralization test (pVNT) that uses a SARS-CoV-2-like virus that expresses the spike protein of SARS-CoV-2 in a viral vector such as vesicular stomatitis virus (VSV) to see if it can inhibit virus growth, and the surrogate virus neutralization test (sVNT) that is strictly a method of detecting binding antibodies that react with the receptor binding domain (RBD) but mimics the measurement of neutralizing antibodies by measuring the degree of inhibition of the interaction of the RBD with ACE-2 [7].

3. Sensitivity and specificity of COVID-19 antibody tests

Early SARS-CoV-2 antibody tests were developed primarily as rapid, simple tests, and suffered from poor sensitivity and specificity, but sensitivity and specificity have improved significantly since those early days [5], and most ELISA and CIA products have sensitivities greater than 95%, and specificities greater than 98% when evaluated using specimens from 2 weeks after infection. The U.S. Food and Drug Administration (FDA) website provides a list of products approved for emergency use and sensitivity and specificity information for each manufacturer's SARS-CoV-2 antibody test products, and as of 30 March 2021, there were 65 approved SARS-CoV-2 antibody test products [8]. As of the end of March 2021, only three products in the form of rapid tests have been approved for use by the Korean Ministry of Food and Drug Safety, but it is expected that more products will be approved for domestic use in the near future. For reference, the sensitivity and specificity criteria for emergency use authorization of SARS-CoV-2 antibody tests in the US, UK, and Canada are shown in **Table 1** [9].

4. Clinical utility of COVID-19 antibody tests and related guidelines

Because the SARS-CoV-2 virus emerged in late 2019 and COVID-19 antibody tests have only been available for about a year, the characteristics of COVID-19 antibody tests are still being studied. We searched for the most current guidelines on the indications and utility of antibody tests, but these are constantly being revised and will likely continue to be revised in the future. In general, viral antibody testing can be used as an adjunctive diagnostic test for infection, to determine a patient's immune status after infection/vaccination, and to determine the prevalence of infection or herd immunity in a population. COVID-19 antibody testing is not recommended for acute diagnosis as an accurate diagnosis in the early stages of infection is critical due to the high transmissibility and lethality of COVID-19 infection but may be used as an adjunctive diagnostic test in clinically strongly suspected cases with negative PCR or antigen tests, in which case an increase in antibody titer or seroconversion in paired blood samples collected 1–2 weeks apart may be diagnostic of infection.

5. A summary of each guideline regarding the usefulness of COVID-19 antibody testing

5.1. Guidelines for the laboratory diagnosis of COVID-19 in Korea

The 4th edition of the Guidelines for the laboratory diagnosis of COVID-19 in Korea, released on 3 December

Table 1. Sensitivity and specificity criteria for the use of SARS-CoV-2 antibody test in the US, UK, and Canada [9]

Country	Sensitivity	Specificity
US FDA	90% overall, 70% IgM, 90% IgG	95% (overall – total)
UK MHRA (the Medicines and Healthcare Products Regulatory Agency)	> 98% (95% CI 96%–100%) on specimens collected 20 days or more after the first appearance of symptoms	> 98% (95% CI 96%–100%)
Health Canada	95% for IgG or total antibodies in samples collected 2 weeks or more after symptom onset	98%

Abbreviations: FDA, Food and Drug Administration; CI, confidence interval.

2020 by the Korean Society of Diagnostic and Laboratory Medicine and the Korea Centers for Disease Control and Prevention, includes indications for COVID-19 antibody testing and states that antibody testing can be performed for the following indications [10]: (1) to investigate the prevalence of antibodies to COVID-19; (2) when past COVID-19 infection is strongly suspected based on epidemiological and clinical findings, but genetic testing is two or more times negative or inconclusive; (3) when multisystem inflammatory syndrome associated with COVID-19 is suspected and performed to differentiate the cause; (4) to screen plasma donors for therapeutic purposes in patients with COVID-19; (5) for entry into countries that require COVID-19 antibody test results upon entry.

5.2. Interim guidelines for COVID-19 antibody testing from the Centers for Disease Control and Prevention (CDC)

Released on 1 August 2020 and revised on 17 March 2021, the interim guidelines were significantly revised throughout [7]. The most significant change in the guidelines is that the August 2020 release stated that to minimize false positives in antibody testing, reagents with high specificity should be used, or used in people with a high probability of antibody positivity, and that the positive predictive value of using only one test is too low, so algorithms that use two tests and test with the second reagent if the first test is positive can be used, etc. In addition, the indications for antibody testing are that a negative antibody test that becomes positive more than 7 days after infection (seroconversion) may be indicative of infection and therefore useful to aid in the diagnosis of COVID-19 and COVID-19 complications, may reflect prior SARS-CoV-2 infection, and may help distinguish between natural infection and vaccination by measuring antibodies to various protein targets. It also states that none of the antibody test products are yet approved for emergency use to assess post-vaccination effectiveness, but does not preclude their use for this purpose. Interpretation of SARS-CoV-2 IgG serology results should be interpreted in the context of vaccination status: in unvaccinated individuals, a positive antibody indicates previous natural infection, In vaccinated individuals, a positive result for antibodies to vaccine-induced antigens, such as the receptor binding domain (RBD) part of the S [S(RBD)] protein, but negative for N-protein antibodies, indicates that vaccination has produced vaccine-induced antibodies and that the individual has never been infected with SARS-CoV-2; and a positive result for N-protein antibodies along with S(RBD) protein antibodies after vaccination indicates SARS-CoV-2 infection before or after vaccination. The key points of the revision are as follows: (1) Antibody tests are not a substitute for virological testing and should not be used to determine the presence or absence of acute SARS-CoV-2 infection; (2) Antibody tests may give different results depending on individual performance characteristics. For public health or clinical purposes, a test product with an Emergency Use Authorization should be used; (3) For antibody tests, either qualitative or semi-quantitative reagents are authorized for emergency use, and there are no public health or clinical indications for which semi-quantitative tests should be given priority; (4) No virus-based neutralizing antibody test has received FDA Emergency Use Authorization, but an ELISA-based competitive neutralizing antibody test has received Emergency Use Authorization. Neutralizing antibody tests are being used as an alternative method of determining defense against infection epidemiologically and clinically; (5) Antibody testing is not currently recommended to assess immunity to COVID-19 after COVID-19 vaccination or to assess the need for vaccination in unvaccinated persons. Because vaccines induce antibodies against specific viral protein targets, post-vaccination serum test results will be negative if the test used does not detect vaccine-induced antibodies; (6) Patients who have a positive antibody test result immediately after contact with a person with confirmed or suspected COVID-19 or

within 3 months before contact and are asymptomatic do not need to isolate. People at increased risk for severe COVID-19 illness, including older adults and people with certain medical conditions, do not need to isolate.

5.3. Infectious Diseases Society of America's guidelines for antibody testing for COVID-19

The Infectious Diseases Society of America's antibody testing guidelines, dated 18 August 2020, outlined eight recommendations [11], which have not been updated to reflect recent CDC revisions and are likely to be revised in the near future. In summary, the guidelines state that antibody testing should not be performed in the first 1–2 weeks of infection because antibody tests may be negative in the first 1–2 weeks of symptoms, and should be performed at 3–4 weeks after symptom onset using IgG or total Ab reagents. In addition, antibody testing may be performed in symptomatic and clinically suspected cases with repeated negative PCR, and simultaneous use of antibody testing and PCR is recommended in patients with pediatric multisystem inflammatory syndrome.

5.4. World Health Organization (WHO) interim guidance for the diagnosis of SARS-CoV-2

Guidance published on 11 September 2020 indicates that antibody testing can be performed on blood samples from the acute phase and 2–4 weeks later in the convalescent phase if both PCR tests are negative and there is clinical suspicion [12]. Seroconversion or an increase in antibody titer in one pair of specimens can be interpreted as a confirmed case.

5.5. International Federation of Clinical Chemistry (IFCC) guidelines

Guidelines published on 7 October 2020 state that it may be used as an adjunct to PCR testing 14 days after symptom onset and to assist in the diagnosis of pediatric multisystem inflammatory syndrome if the PCR test remains positive in recovering patients [13]. It may also be useful in the following cases for which there is insufficient evidence: diagnosis of past infections, quantification of antibody response in patients with COVID-19, screening of plasma donors, assessment of immune status and antibody response to vaccines, and monitoring of herd immunity. However, it is not recommended for diagnostic purposes in the acute phase before 14 days and is recommended when symptoms are present and the PCR is negative.

5.6. Canadian antibody testing guidelines

Canadian antibody testing guidelines released on 14 December 2020 list the following indications for antibody testing for which there is evidence: diagnosis of past infection; as an adjunctive diagnostic when nucleic acid testing (NAT) is negative or inconclusive; to determine seroprevalence in a population; as contact tracing; in the diagnosis of pediatric multisystem inflammatory syndrome; to identify plasma donors; and to assess vaccine response [14].

6. Conclusion

This article summarized the current status of COVID-19 antibody testing as well as the domestic and international guidelines for the testing. The negative aspects of antibody testing for COVID-19 have been highlighted due to the relatively high false-positive rate of early development reagents and false-negative results in the early stages of infection due to the highly fatal and contagious nature of the disease. However, as more concrete data on antibody testing has been accumulated, the utility of antibody testing in complementary diagnostics to PCR, identification of recent/previous infections, determination of post-vaccination efficacy, policy-making through seroprevalence surveys, and donor screening for plasma therapies has been rediscovered. However, much remains to be learned

about antibody testing, including which antigens and epitope sites are ideal as target antigens for SARS-CoV-2 antibody testing, the duration of different types of antibodies, the relationship between antibody production and immunity, changes in antibodies after vaccination, differences in immune response between vaccine types, and variants and antibody testing. As more specific data and knowledge are accumulated and the benefits and limitations of individual antibody tests become clearer, SARS-CoV-2 antibody tests will become more useful in the clinic.

Disclosure statement

The author declares no conflict of interest.

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