

BRIEF REVIEW

The Role of Rapid Diagnostic Point of Care IgG/IgM Antibody Tests in the Diagnosis of SARS-CoV-2 Infection

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Abstract

Background: Current testing of symptomatic patients for SARS-CoV-2 involves the use of nucleic acid amplification tests, also known as genetic, RNA, or polymerase chain reaction (PCR), to detect viral RNA. The initial use of point of care (POC) antibody tests, also known as serological tests, in the management of SARS-CoV-2 infection was limited. In this review, we determine the significance of POC antibody serological tests and explore their possible role in the diagnosis and management of patients infected with the SARS-CoV-2 virus.

Methods: A literature search was conducted in Google Scholar, PubMed, and Embase, supplemented by searching the Centers for Disease Control and Prevention (CDC) and Infectious Diseases Society of America (IDSA) websites. We identified seven articles published in the last six months pertaining to our search. The sensitivity and specificity statistics of IgG/IgM antibody tests obtained from these studies were

compared and used to determine the clinical importance of rapid diagnostic antibody tests for SARS-CoV-2.

Results: Through the literature review, it was found that POC diagnostic antibody tests can be used as an adjuvant with nucleic acid amplification tests in determining both active and post-exposure antibodies. These rapid antibody IgG/IgM tests had high sensitivity—the ability of a test to correctly identify those with the disease—and high specificity—the ability of a test to correctly identify those without the disease.

Conclusion: Emerging studies indicate the importance of POC antibody serological testing as a diagnostic tool in the current SARS-CoV-2 pandemic. Considering the limitations of the molecular methods of testing, POC antibody tests can help reduce dependency on molecular assays when used in conjunction with them.

Introduction

IgG and IgM are among the different types of antibodies produced during an immunological response to a pathogen. Detection of IgM in the body indicates a recent infection while the presence of IgG indicates a prior exposure to the same pathogen or a chronic infection. The two major antigenic targets of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus against which antibodies are detected are spike glycoprotein (S) and nucleocapsid phosphoprotein (N). As per CDC, SARS-CoV-2 infection is unusual as there is simultaneous appearance of both IgG and IgM antibodies in the serum within 2-3 weeks after the onset of illness. Therefore, detection of IgM without IgG is uncommon during this timeframe.[1] Studies indicate that serological tests can detect the presence of SARS-CoV-2 IgG and IgM antibodies as early as day 4 after symptom onset, however, antibodies could be also be detected in

the middle and later course of the disease.[2] Most patients seroconvert around 7-11 days post-exposure to the virus.[3] One study found that the IgM antibodies initially increased followed by a decline while the IgG antibody levels stabilized over time. IgG antibody levels were also found to double after the PCR resulted negative.[4] Another study found that the average levels of IgM and IgA antibodies increased within 6-8 days from the onset of symptoms. Compared to the IgM antibody, IgA antibody showed persistently higher levels for the whole observation period, with a peak level at 20-22 days.[5] The detection of the antibodies collectively at the time when the PCR becomes negative implied that they may have a role in the clearance of the virus.[2] While one study linked the appearance of antibodies with the severity of the disease, another study revealed that it may be independent of the clinical course of the disease.[6] It was also found that high antibody levels may help in the progression of the in-

fection as high viral load lead to strong extra-follicular B cell stimulation leading to rapid antibody production which doesn't follow the sequential change from IgM to IgG. Such antibodies stimulate cytokine storm which has been implicated in acute lung injury associated with COVID-19 infection.[6] Many patients were found to be seropositive within the course of illness for more than 30 days.[2] However, a negative serological test does not exclude COVID-19 infection as many patients were found to be seronegative during the early course of the infection.[4] Hence the results of these serological assays may be inconclusive during the early course of the disease.

The CDC categorizes antibody tests into two broad categories: 1) Binding antibody detection tests and 2) neutralizing antibody tests. While the use of neutralizing antibody tests has not been approved by the US-FDA, the binding antibody tests are widely employed in the detection of the IgG and IgM antibodies. These tests detect the presence of different types of antibodies against different components of the SARS-CoV-2 virus using purified proteins of the virus. Specific reagents are used to identify individual antibody types such as IgG, IgM, and IgA. These tests are further classified into point of care tests (POC) such as lateral flow immunochromatography assays (LFIA) and laboratory-based tests such as Enzyme-linked immunosorbent assay (ELISA) and chemiluminescent assay (CIA). POC tests are performed at the time and place of patient care such as the patient's bedside or the physician's office. These tests use lateral flow devices to detect IgG or IgG and IgM or total antibody in serum, plasma, whole blood, saliva. While the POC tests can be performed in a field setting, lab-based tests require trained laboratorians and a specialized setting. IgG/IgM rapid tests are the two available point of care, qualitative antibody detection tests.[1]

The current recommendations of the CDC heavily depend upon the use of reverse transcriptase polymerase chain reaction (RT-PCR) for the qualitative detection of SARS-CoV-2 viral nucleic acid for the diagnosis and the management of the COVID-19. In the wake of the increasing emergence of challenges and limitations of the molecular tests, the importance of rapid diagnostic antibody tests has increased, and their role is being rapidly explored.[7] In our review, we explore the role of the POC antibody tests.

Methods

For our article, literature contained in Google Scholar, PubMed, and Embase, as well as websites for the Center for Disease Control (CDC) and the Infectious Diseases Society of America (IDSA) database, was searched using combinations of keywords 'SARS-CoV-2', 'coronavirus', 'COVID-19 pandemic', 'health care

workers', 'molecular test', 'diagnostic tests', 'serological tests' and their variants. The articles used for the review were published within the last 6 months (December 2019 to June 2020).

Results

Seven studies were eligible for inclusion in this review. All the included studies used immunochromatography method of POC IgG/IgM antibody test. The tests were conducted on blood or plasma or serum samples. Spicuzza et al, Ying et al, Zhengtu et al, Dohla et al, and Choe et al used combined IgG/IgM antibody kit and divided patients in two groups.[8-12] One group had patients who tested positive for SARS-CoV-2 using RT-PCR while the second group had patients who were suspected of having COVID-19 infection, but tested negative on an RT-PCR. Hoffman et al conducted the study by dividing their patients in a similar manner, but they used rapid IgG-IgM detection test which detected IgG and IgM antibody separately.[13] While Xiang et al also used rapid IgG-IgM antibody detection kit detecting the antibodies separately, they tested patients diagnosed with a positive viral RT-PCR in both groups.[14] They tested one of the groups with laboratory-based ELISA antibody test while the other group was tested using the rapid IgG-IgM POC antibody test. These studies calculated the sensitivities and specificities of the test, which can be seen in **Table 1**.

Discussion

It was observed that the overall sensitivity and specificity of these antibody tests was high except for Dohla et al. The antibody tests also yielded high sensitivity and specificity for the detection of individual IgG/IgM antibodies. The results indicate that these tests could play a very important role in diagnosis of SARS-CoV-2 infection when used in conjunction with the molecular tests. The rapid diagnostic POC test could be preferred over the laboratory-based antibody test. Hence, the rapid diagnostic IgG/IgM antibody tests can be used in conjunction with the molecular test. These tests are faster, less expensive, easy to use, accessible to staff without lab training and are higher specificity versus the laboratory-based antibody test.[2, 4, 15] These antibody tests have also been found to be beneficial in diagnosing patients with a prolonged clinical course. They can be used to diagnose patients with a prolonged course of illness, who get a false negative result on the PCR.[2] They can diagnose patients who have recovered from a prior asymptomatic infection. These asymptomatic patients may have a positive IgG, a negative IgM, a negative molecular test with no prior history of COVID-19 infection.[16] POC antibody tests can also be used for contact tracing, serological surveil-

Table 1. Studies considered for our review.

Authors	Results	Summary
1 Spicuzza et al	<p>Sample size: 37</p> <p>Sensitivity: 82.6%</p> <p>Specificity: 92.8%</p>	<p>In patients presenting with a discrepancy between the clinical/radiological feature and the molecular test, the rapid antibody detection might be an additional element helping the clinician to make a correct diagnosis</p>
2 Xiang et al	<p>Sample size: 179</p> <p>Sensitivity: 85% (77/90)</p> <p>Specificity: 91% (8/89)</p>	<p>The sensitivity and specificity of the IgG/IgM combined test kit is adequate, with short turnaround time, no specific requirements for additional equipment or skilled technicians, all of these collectively contribute to its competence for mass testing. At the current stage, it cannot replace SARA-CoV-2 nucleic acid RT-PCR, but it can serve as a complementary option with RT-PCR.</p>
3 Yan et al	<p>Sample size: 154</p> <p>Sensitivity: 82(75/91)</p> <p>Specificity: 100% (35/35)</p>	<p>Although ELISA and GICA are simple, fast, and safe, the results can be used for clinical reference</p>
4 Hoffman et al	<p>Sample size: 153</p> <p>Sensitivity (IgM): 69% (20/29)</p> <p>Sensitivity (IgG): 99% (27/29)</p> <p>Specificity (IgM): 100% (124/124)</p> <p>Specificity (IgG): 99% (123/124)</p>	<p>The test is suitable for assessing previous virus exposure, although negative results may be unreliable during the first few weeks after infection.</p>
5 Zhengtu et al	<p>Sample size: 397</p> <p>Sensitivity: 89% (352/397)</p> <p>Specificity: 91% (12/128)</p>	<p>The IgM-IgG combined assay has better utility and sensitivity compared with a single IgM or IgG test. It can be used for the rapid screening of SARS-CoV-2 carriers, symptomatic or asymptomatic, in hospitals, clinics, and test laboratories</p>
6 Dohla et al	<p>Sample size: 49</p> <p>Sensitivity: 36.4%</p> <p>Specificity: 90%</p>	<p>Rapid antibody test have low sensitivity and is not recommended for community screening.</p>
7 Choe et al	<p>Sample size: 149</p> <p>Sensitivity: 93%(95% CI: 84.1-97.6)</p> <p>Specificity: 96.2%(95% CI: 89.3-99.2)</p>	<p>The immunochromatography-based COVID-19 IgG/IgM rapid test is a useful and practical diagnostic assay for practical diagnostic assay for detection of COVID-19, especially in the presence of IgM or IgG antibodies.</p>

lance at local, regional, state, and national levels. They can identify possibly immune patients and individuals who could be a source of therapeutic or prophylactic neutralizing antibodies and vaccine trials.[15, 17] How-

ever, the use of these assays cannot be used to determine immune status in individuals until the presence, durability and duration of immunity is established.[1]

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