University of Louisville Journal of Respiratory Infections

BRIEF REVIEW

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

Nishita Tripathi[1], MD; Daniya Sheikh[1], MD; Dawn Balcom[1], DNP*

[1] Division of Infectious Diseases, University of Louisville School of Medicine, Louisville, KY, USA

*nishita.tripathi@louisville.edu

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 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 SARS-CoV-2 virus.

Methods: A literature search was conducted in Google Scholar, PubMed, and Embase, and supplemented by searching the Center for Disease Control (CDC), and the Infectious Diseases Society of America (IDSA) websites. We identified 7 articles published in the last 6 months pertaining to the keywords. The sensitivity and specificity of the IgG/IgM antibody tests obtained from these studies were compared and used to determine the clinical importance of the rapid diagnostic antibody test in SARS-CoV-2 infection.

Results: Through the literature review, it was found that POC diagnostic antibody tests can be used as an adjuvant with the 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 the test to correctly identify those without the disease.

Conclusion: Emerging studies indicate the importance of POC antibody serological testing as an important 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 the molecular assays of testing when used in conjunction with them.

Recommended Citation:
Tripathi, Nishita; Sheikh, Daniya; and Balcom, Dawn (2020). "The Role of Rapid Diagnostic Point of Care IgG/IgM Antibody Tests in the Diagnosis of SARS-CoV-2 Infection," *The University of Louisville Journal of Respiratory Infections*: Vol. 4, Iss. 1, Article 70.

Received Date: September 4, 2020

Accepted Date: November 4, 2020

Published Date: November 23, 2020

Funding Source: The author(s) received no specific funding for this work.

Conflict of Interest: All authors declared no conflict of interest in relation to the main objective of this work.

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 infection 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 by 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 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**.

Table 1. Studies considered for our review.

S.no	Author	Title	Result	Summary
1	Spicuzza et al	Reliability and usefulness of a rapid IgM-IgG antibody test for the diagnosis of SARS-CoV-2 infection: A preliminary report.	Sample size-37 Sensitivity=82.6% Specificity=92.8%	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
2	Xiang et al	Diagnostic Indexes of a Rapid IgG/IgM Combined Antibody Test for SARS-CoV-2	Sample size-179 Sensitivity- 85% (77/90) Specificity- 91% (8/89)	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.
3	Yan et al	Evaluation of Enzyme-linked Immunoassay and Colloidal Gold Immunochromatographic Assay kit for detection of novel coronavirus (SARS-CoV-2) causing an outbreak of pneumonia (COVID 19)	Sample size-154 Sensitivity- 82(75/91) Specificity- 100% (35/35)	Although ELISA and GICA are simple, fast, and safe, the results can be used for clinical reference
4	Hoffman et al	Evaluation of a COVID-19 IgM and IgG rapid test; an efficient tool for assessment of past exposure to SARS-CoV-2	Sample size - 153 Sensitivity- Ig M: 69% (20/29) Ig G-99% (27/29) Specificity- Ig M-100% (124/124) Ig G- 99%(123/124)	The test is suitable for assessing previous virus exposure, although negative results may be unreliable during the first few weeks after infection.
5	Zhengtu et al	Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis	Sample size-397 Sensitivity- 89% (352/397) Specificity- 91% (12/128)	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
6	Dohla et al	Rapid point-of-care testing for SARS-CoV-2 in a community screening setting shows low sensitivity	Sample size-49 Sensitivity- 36.4% Specificity- 90%	Rapid antibody test have low sensitivity and is not recommended for community screening.
7	Choe et al	Diagnostic performance of immunochromatography assay for rapid detection of IgM and IgG in coronavirus disease 2019	Sample size- 149 Sensitivity- 93% (95% CI: 84.1-97.6) Specificity- 96.2% (95% CI: 89.3-99.2)	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.

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. [4,2,15] 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 surveillance 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] However, 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]

References

1. Centers for Disease Control and Prevention [Internet]. New York, NY: Oxford University Press; Interim Guidelines for COVID-19 Antibody Testing: Interim Guidelines for COVID-19 Antibody testing in Clinical and Public Health Settings; [Updated 2020 Aug 1] Available from: https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html
2. Xiang F, Wang X, He X, Peng Z, Yang B, Zhang J, et al. Antibody detection and dynamic characteristics in patients with COVID-19. Clin Infect Dis [Journal on the Internet]. 2020 Apr 19;71(8):1930-1934.
3. Patel R, Babady E, Theel ES, Storch GA, Pinsky BA, St George K, et al. Report from the american society for microbiology covid-19 international summit, 23 march 2020: value of diagnostic testing for sars–cov-2/covid-19. MBio. 2020 Mar;11(2):e00722-20. https://doi.org/10.1128/mBio.00722-20 PMID:32217609
4. Jin Y, Wang M, Zuo Z, Fan C, Ye F, Cai Z, et al. Diagnostic value and dynamic variance of serum antibody in coronavirus disease 2019. Int J Infect Dis. 2020 May;94:49–52. https://doi.org/10.1016/j.ijid.2020.03.065 PMID:32251798
5. Padoan A, Sciacovelli L, Basso D, Negrini D, Zuin S, Cosma C, et al. IgA-Ab response to spike glycoprotein of SARS-CoV-2 in patients with COVID-19: a longitudinal study. Clin Chim Acta. 2020 Aug;507:164–6. https://doi.org/10.1016/j.cca.2020.04.026 PMID:32343948
6. Yongchen Z, Shen H, Wang X, Shi X, Li Y, Yan J, et al. Different longitudinal patterns of nucleic acid and serology testing results based on disease severity of COVID-19 patients. Emerg Microbes Infect. 2020 Dec;9(1):833–6. https://doi.org/10.1080/22221751.2020.1756699 PMID:32306864
7. Tahamtan A, Ardebili A. Real-time RT-PCR in COVID-19 detection: issues affecting the results. Expert Rev Mol Diagn. 2020 May;20(5):453–4. https://doi.org/10.1080/14737159.2020.1757437 PMID:32297805
8. Spicuzza L, Montineri A, Manuele R, Crimi C, Pistorio MP, Campisi R, et al. Reliability and usefulness of a rapid IgM-IgG antibody test for the diagnosis of SARS-CoV-2 infection: A preliminary report. J Infect. 2020 Aug;81(2):e53–4. https://doi.org/10.1016/j.jinf.2020.04.022 PMID:32335175
9. Liu Y, Liu Y, Diao B, Ren F, Wang Y, Ding J, et al. Diagnostic Indexes of a Rapid IgG/IgM Combined Antibody Test for SARS-CoV-2. medRxiv. 2020 Mar 30.
10. Li Z, Yi Y, Luo X, Xiong N, Liu Y, Li S, et al. Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis. J Med Virol. 2020 Feb;92(9):1–7. https://doi.org/10.1002/jmv.25727 PMID:32104917
11. Döhla M, Boesecke C, Schulte B, Diegmann C, Sib E, Richter E, et al. Rapid point-of-care testing for SARS-CoV-2 in a community screening setting shows low sensitivity. Public Health. 2020 May;182:170–2. https://doi.org/10.1016/j.puhe.2020.04.009 PMID:32334183
12. Choe JY, Kim JW, Kwon HH, Hong HL, Jung CY, Jeon CH, et al. Diagnostic performance of immunochromatography assay for rapid detection of IgM and IgG in coronavirus disease 2019. J Med Virol. 2020 May;92(11):2567–72. https://doi.org/10.1002/jmv.26060 PMID:32458479
13. Hoffman T, Nissen K, Krambrich J, Rönnberg B, Akaberi D, Esmaeilzadeh M, et al. Evaluation of a COVID-19 IgM and IgG rapid test; an efficient tool for assessment of past exposure to SARS-CoV-2. Infect Ecol Epidemiol. 2020 Apr;10(1):1754538. https://doi.org/10.1080/20008686.2020.1754538 PMID:32363011
14. Xiang J, Yan M, Li H, Liu T, Lin C, Huang S, et al. Evaluation of enzyme-linked immunoassay and colloidal gold-immunochromatographic assay kit for detection of novel coronavirus (SARS-Cov-2) causing an outbreak of pneumonia (COVID-19). MedRxiv. 2020 Mar 1.
15. Kenyon C. The serostatus approach to fighting COVID-19. Int J Infect Dis. 2020 May;94:53–4. https://doi.org/10.1016/j.ijid.2020.03.080 PMID:32276044
16. Wu X, Fu B, Chen L, Feng Y. Serological tests facilitate identification of asymptomatic SARS-CoV-2 infection in Wuhan, China. J Med Virol. 2020 Apr;92(10):1795–6. https://doi.org/10.1002/jmv.25904 PMID:32311142
17. Amanat F, Stadlbauer D, Strohmeier S, Nguyen TH, Chromikova V, McMahon M, et al. A serological assay to detect SARS-CoV-2 seroconversion in humans. Nat Med. 2020 Jul;26(7):1033–6. https://doi.org/10.1038/s41591-020-0913-5 PMID:32398876