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Research Article

Sensitivity and Specificity of Gold Chromatography Immunoassays IgM/IgG Antibody Test for COVID-19: Review of the Current Literature

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Abstract

Background: The World Health Organization recommends molecular tests Polymerase Chain Reaction (PCR) to the diagnosis of coronavirus disease of 2019 (COVID-19), which detect the Severe Acute Respiratory Syndrome (SARS-Coronavirus 2) virus RNA. However, these tests are expensive and give a high negative result. There were urgent medical and public health needs for early diagnosis and treatment to minimize the spread of COVID-19. This review aimed to summarize known to date information about the latest research progress of the sensitivity and specificity of rapid combined IgM/IgG antibody test to diagnose the pandemic novel coronavirus disease of 2019 (COVID-19).

Methods: Databases such as PubMed, Google Scholar, Science Direct, Web of Science electronic databases were search related articles published between January 23, 2020 and April 29, 2020, using the following search terms: "COVID19 or COVID-19," "novel coronavirus," "SARS CoV-2 or SARS CoV2," "Rapid antibody test," "IgM/IgG," "sensitivity," "specificity."

Results: The review included eight clinical studies for a total of 782 patients with COVID-19 and 631 healthy controls. The sensitivity and specificity of gold chromatography immuno-assays (GCIAs) IgM/IgG rapid test vary greatly among published studies. Of the eight shortlisted studies, the IgM/IgG sensitivity ranged from 73.9% to 89.3% in six (75%) and the IgM/IgG specificity ranged from 88.9% to 100% in the eight (100%) reviewed studies. The pooled data revealed that the average sensitivity and specificity was 70% and 94.5%, respectively. They agreed on its simplicity, fastness, and fewer requirements.

Conclusion: The GCIAs IgM/IgG rapid tests are simply fast and safe. Besides their short turnaround time, no specific equipment or skilled technicians' requirements, they can serve as a rapid diagnostic test of RT–PCR-negative highly suspected patients and screening of SARS CoV-2 carriers. It cannot take the place of PCR, but the huge lab diagnosis pressure can be greatly relieved and more research is needed to detect its reliability and clinical utility in limited-resource settings.

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Keywords: COVID-19, Rapid Test, IgM/IgG, sensitivity, specificity, limited-resource

1. Introduction

Coronavirusesare a large group of viruses that belong to *Coronaviridae* family. These viruses are enveloped RNA viruses, surrounded by a club-like projection (spikes) on the outer surface, which give the virus a crown-shaped appearance [1]. They were known to cause acute respiratory diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) [2].

The World Health Organization officially named the novel coronavirus 2019-nCoV as SARS CoV-2 and the disease as coronavirus disease 19 (COVID-19) [3]. On December 12, 2019, patients with pneumonia of unknown origin were identified, which was followed by an outbreak in Wuhan city, China on December 31, 2019. The Chinese Center for Disease Control and Prevention (China CDC) detected the novel coronavirus in samples of the lower respiratory tract from patients with pneumonia and discovered the genomic sequence on January 11, 2020. On March 11, 2020, the WHO declared COVID19 outbreak a global pandemic [4]. As of April 29, 2020, WHO had reported 2,954,222 confirmed cases and 202,597 death worldwide [5]. Bats have been suspected as the natural host origin of the virus by several studies, and is transmitted to humans through unknown intermediate host[6]. The disease is highly infectious, and human-to-human transmission occurs due to close contact with a person with respiratory symptoms such as sneezing and coughing. The aerosols and droplets reach the lungs through inhalation via the mouth and nose [2] . Also, fecal-oral transmission and transmission via vomits have been reported [7, 8].

The clinical features of COVID-19 are highly nonspecific and varied, ranging from asymptomatic to severe pneumonia, respiratory failure, and even death in certain cases [4, 9]. The main symptoms reported were sore throat, dry cough, fever, chills, headache, fatigue, muscle and joint pain, sputum production, shortness of breath, conjunctival and nasal congestion [4, 10]. The digestive symptoms such as diarrhea, nausea, or vomiting cab be an early sign of infection [11]. Approximately 80% of the people infected with SARS CoV-2 had mild to moderate disease and recovered, which includes pneumonia and non-pneumonia cases. The evere disease was reported to have occurred in about 13.8% and the symptoms included dyspnea or high respiratory rate ($\geq$ 30 breath/min), low pulse oxygen saturation ($\leq$ 93%), and low PaO2/FiO2 ratio ($<$ 300). About 6.1% represent the critical cases that include respiratory failure, septic shock, and multiple organ dysfunction [12]. The high-risk factors for severe disease and death include cancer, people aged $>$ 60 years, and chronic diseases such as cardiovascular disease, diabetes, hypertension, and chronic respiratory disease [4, 15]. The disease in children aged $<$ 19 years was rare and mild, and a very small proportion of them developed severe or critical condition [4, 12, 14].

The diagnosis of COVID-19 is based on clinical symptoms, epidemiological history, and auxiliary examination such as Real Time-PCR (RT-PCR) for virus nucleic acid, CT

imaging, liver enzymes, serological tests, blood culture, and some hematological parameters [16]. However, since the clinical manifestations were highly atypical, auxiliary examinations were necessary as primary tools for the diagnosis [17].

Currently, RT-PCR for virus nucleic acid (RNA) is considered as the gold standard for detecting SARS Cov-2 [18]. The RNA virus is detected using lower and upper respiratory samples. The upper respiratory samples such as nasopharyngeal swabs, oropharyngeal swabs, nasopharyngeal washes, and nasal aspirates were recommended in the reviewed studies. However, the lower respiratory samples such as sputum, endotracheal aspirates, and Broncho Alveolar Lavage were recommended for patients with productive cough (19). In severe cases, the virus nucleic acid (RNA) may also be detected in the stool (9). Although RT-PCR is considered as a standard method for the diagnosis because they identify the specific sequence of the pathogen, it also has a high false-negative rate [19, 20].

As an alternative to RT-PCR, computed tomography (CT scan) can also be used for the clinical diagnosis of COVID-19, as a CT scan is more sensitive and specific, and can therefore be used to diagnose asymptomatic and suspect patients with negative molecular diagnosis [9]. Overall, CT imaging revealed infiltrates, ground glass appearance, and consolidation with or without vascular enlargement [21], as well as interlobular septal thickening, in comparison to images of healthy lungs [22].

Generally, the laboratory examination results are highly non-specific. The white blood cell counts (WBCs) and the platelet count were usually normal or decreased with lymphopenia [6]. The level of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were generally elevated [23]. However, in severe cases, neutrophils counts were high whereas lymphocyte counts were low [6]. The level of alanine aminotransferase (ALT), aspartate aminotransferase (AST), procalcitonin, prothrombin time, creatinine, D-dimer, creatine phosphokinase (CPK), and lactate dehydrogenase (LDH) were increased [24, 25].

Several serological tests for the measurement of specific IgM/IgG antibody in sera of COVID-19 patients developed and were pre-tested by some companies, such as Enzyme-linked Immunosorbent Assay (ELISA), Chemiluminescence Immunoassay (MAGLUMI 2000 Plus CLIA), and Point of Care Testing (POCT), but very few articles were published. While immunoglobulin IgG indicates recent and past infection, IgM indicates current infection [26]. The serological test may help in the diagnosis of a patient suspected with COVID-19 with a negative RT-PCR result and in the documentation of asymptomatic infection [23]. The sensitivity of the assay is the ability to correctly detect positive cases, whereas specificity is the ability to correctly detect negative cases. So, highly sensitive test means there were few false-negative results and a highly specific test mean there were few false-positive results [27]. There are urgent medical and public health needs of a sensitive and specific test for the early diagnosis and treatment to minimize the spread of COVID-19.

2. Materials and Methods

A search was run for articles on COVID-19 by using electronic databases such as PubMed, Google Scholar, Science Direct, supplemented by Web of Science electronic databases, using the following search terms: “COVID19 or COVID-19,” or “novel coronavirus,” “SARS CoV-2,” “SARS CoV2,” “rapid antibody test,” “IgM/IgG,” “sensitivity,” and “specificity.” The full-text articles were identified and screened for original data. The reference lists were retrieved and checked manually for further relevant studies. Studies were included when the article was published in the English language and referred to humans.

3. Results

The studies were retrieved between January 23, 2020 and April 29, 2020. A total of 142 titles were retrieved, and after removing duplication and excluding articles that did not meet the inclusion criteria, eight studies were included in the review and considered as eligible.

In the eight included studies, a total of 782 cases were reported, of which, 707 were confirmed cases for COVID-19 by PCR, 75 were negative PCR but with signs of COVID-19, and 631 were healthy controls (see Table 1). The study populations of the three studies were grouped according to the time of disease onset. Six studies detected SARS CoV-2 IgM/IgG antibody in serum, whereas two studies detected it in whole blood. All studies considered PCR as the gold standard. Only one study imported from Denmark aimed to evaluate the sensitivity and specificity of six commercially available points of care IgM/IgG rapid tests and the rest of the studies were imported from China aimed to evaluate commercially available point of care IgM/IgG rapid test, see Table 2.

Table 1: Sensitivity and specificity of combined IgM/IgG rapid tests

No.	Author	Study population			Sensitivity%	Specificity%
		PCR+ve	PCR–ve	Healthy	IgM/IgG	IgM/IgG
1	(Li *et al*., 2020) [27]	397		128	88.7	90.3
2	(Hoffman *et al*., 2020) [28]	29		124	81.1	99.6
3	(Cassaniti *et al*., 2020) [29]	38	12	30	18.4	91.7
4	(Dohla *et al*., 2020) [30]	39		10	36.4	88.9
5	(Ying *et al*., 2020) [31]	90		89	85.6	91
6	(Xiang *et al*., 2020) [32]	29		124	82.4	100
7	(Perez *et al*., 2020) [33]	55	63	45	73.9	100
8	(Lassauniere *et al*., 2020) [34]	30		81	89.3	94.5

4. Discussion

Although, currently, RT PCR is considered as a gold standard test for COVID-19, this technique is expensive, requires high-quality and well-equipped laboratory facilities,

Table 2: Manufacturer information of IgM/IgG rapid test

No.	Reference No.	Product Name
1	[27]	SARS Cov-2 Rapid IgG/IgM combined antibody Test Kit/Jiangsu Medomics Medical Technologies, Nanjing, China.
2	[28]	COVID19 IgG/IgM Rapid Test Cassette/Zhejiang orient Gene Biotech Co. Ltd, Huzhou, Zhejiang, China.
3	[29]	VivaDiag COVID19 IgM/IgG Rapid Test/Vivacheck Biotech Co. Ltd, China.
4	[30]	Not mentioned
5	[31]	SARS cov-2 IgG/IgM Antibody Test Kit/Chinese Biotechnology Company, China.
6	[32]	Novel Coronavirus IgG/IgM Antibody GICA Kit/Zhu Hai Liv Zon Diagnostic Inc., China.
7	[33]	COVID19 IgG/IgM/All Test Biotech, Hangzhou, China.
8	[34]	2019 n COV IgG/IgM Rapid test/Dynamiker Biotechnology, Tianjin, China. Anti-SARScov-2 Rapid Test/Auto Bio Diagnostics, Zhengzhou, China. 2019 n COV IgG/IgM Rapid test cassette/Hangzhou All test Biotech, Hangzhou, China. On-Site TM COVID19 IgG/IgM Rapid Test/CTK Biotech, Poway, CA, USA. 2019 n COV IgG/IgM Rapid Test Cassette/Acro Biotech, Rancho Cucamonga, CA, USA. Coronavirus Diseases 2019 (COVID19) IgG/IgM Antibody Test/Artorn Laboratories, Burnaby, Canada.

trained staff, and has a high false-negative results rate [19, 20, 25]. The possible explanation for the high false-negative results is that SARS CoV2 infection mainly occurs in the lungs (lower respiratory tract), whereas the samples are taken mostly from the upper respiratory tract. Wang *et al*. reported that the RT-PCR of nasal and pharyngeal swab detected virus only in two-third and one-third of cases, respectively, and the rates of the positive result were 63% and 32%, respectively, when compared to Broncho-alveolar lavage fluid and sputum, 93% and 72%, respectively [36]. However, according to Ren *et al*., the sensitivity and specificity of RT-PCR for pharyngeal swab were 98.8% and 78.2%, respectively [37].

The GCIA, on the other hand, is a rapid serological test for the detection of IgM/IgG combined antibody of SARS CoV2, and can give the result in less than 15 min without the requirement of high-quality and well-equipped laboratory facilities, trained staff, or specimen transportation as compared to PCR [32]. It remains a good choice in developing countries such as Sudan. IgM antibody can be detected in the blood specimen after three–six days, while IgG is detected after eight days of disease onset (38). The current review showed that eight studies used the GCIA for the IgM/IgG antibody. The GCIA is simple and provides a rapid diagnosis for COVID19. However, when the specimen is collected in the early stage of the disease onset, the false-negative result rate was high [15].

Further, Li *et al*. reported the sensitivity and specificity of IgM/IgG as 88.7% and 90.6%, respectively. They explained that the false-negative was due to low antibody concentration, the differences in immune response between individuals, decrease and disappeared IgM antibody after two weeks, and difficulties in knowing the exact time of infection [28]. Likewise, Xiang *et al*. reported a sensitivity and specificity of IgM/IgG as

82.4%, and 100%, respectively [33]. Hoffman *et al*., in their study, found the sensitivity of IgM and IgG to be 69% and 93.1% and the specificity to be 100% and 99.2%, respectively. They observed one false-positive result for IgG from healthy control group sample collected in 2018; this result indicates cross-reaction between SARS-CoV and SARS-CoV2 or another human coronavirus [29].

Further, Hoffman *et al*. grouped the patients into two categories according to the time of disease onset and found no significant difference in the IgM and IgG between the two groups. They concluded that the performance of IgM/IgG rapid test was satisfactory [29]. Also, Perez *et al*. and Ying *et al*. found that the sensitivity and of IgM/IgG were 73.9% and 82.4% and the specificity were 100% and 100%, respectively. Perez *et al*. and Ying *et al*. categorized the cases into three groups according to the time of disease onset and found an increase in the positivity rate for IgM/IgG from 7–13 days to ≥ 14 days [32, 34].

Although Lassauniere *et al*. used the same kit as Perez *et al*., the sensitivity and specificity was, however, 100% and 87%, respectively. These differences may probably be due to the differences in the setting or the study population [34, 35]. Perez *et al*. concluded that the immune-chromatography test is considered as a reliable diagnostic test for SARS CoV2 infection from 14 days of disease onset [34], and Ying *et al*. concluded that the sensitivity and specificity of the GCIA for IgG/IgM combined test were good [32].

On the other hand, Cassaniti *et al*. and Dohla *et al*. found that the sensitivity and specificity of IgM/IgG were 18.4% and 36.4%, and 91.7% and 88.9%, respectively, and additionally due to poor sensitivity, they concluded that COVID19 IgM/IgG rapid diagnostic test is not recommended for a patient with suspected COVID-19 [30, 31]. Perhaps, the low sensitivity may be due to samples taken in the early onset of the disease. Dohla *et al*. recommend the acceleration of improvement and assessment of the effective point of the care test system [31]. Currently, the available serological tests use antibodies against either nucleocapsid protein (N) or spike protein (S) on the surface of SARS COV-2 [39]. Previous studies reported that the sensitivity and specificity of assays that used antibodies against S protein were high because the S protein is highly immunogenic and its affinity to angiotensin-converting enzyme receptor2 (ACE2) correlated with infectivity [40, 41]. Hence, IgM/IgG tests may be of help for the diagnosis when there is a positive test result accompanied with repeated negative RT-PCR in a highly suspected patient and for rapid screening of SARS CoV-2 carriers in limited-resource countries like Sudan where people are used to present late. Also, it can be used to screen health workers following isolation and for management using convalescence plasma. Additionally, the huge laboratory diagnosis pressure can be greatly relieved; also giving value to the diagnosis and treatment.

5. Limitations

The main limitation of the current study was that seven studies were from the same country (China) and only one from Denmark. Not all studies grouped the population according to disease onset. There were differences in sample size and the type of SARS

CoV-2 antigen targeted in assay between the studies. The cross-reactivity between SARS-CoV and another human coronavirus might have happened.

6. Conclusion

The sensitivity and specificity of the GCIA for IgM/IgG vary greatly among published studies. Of the eight reviewed studies, the IgM/IgG sensitivity ranged from 73.9% to 89.3% in six (75%) and from 88.9% to 100% in all the reviewed studies (100%). They agreed that IgM/IgG rapid test are good, as besides being rapid, they do not need any special equipment or skilled staff. Although it cannot replace PCR, it can serve as a rapid diagnostic test for RT-PCR-negative highly suspected patients and screening of SARS CoV-2 carriers in limited-resource countries, and the massive laboratory diagnosis pressure can be highly relieved. Furthermore, it can be used for management using convalescent plasma and screening of health workers following isolation. More research is needed to detect its reliability and clinical utility in limited-resource settings.

Conflicting Interest

There is no conflict of interest.

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