Should IgM/IgG rapid test kit be used in the diagnosis of COVID-19?

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This rapid review summarizes the available evidence on the sensitivity, specificity, and appropriate schedule of IgM/IgG rapid test kit in diagnosing COVID-19. This may change as new evidence emerges.

KEY FINDINGS

Current evidence does NOT support use of IgM/IgG rapid test kits for the definitive diagnosis of COVID-19 in currently symptomatic patients.

- The present standard for diagnosis of COVID-19 is through qualitative detection of COVID-19 virus nucleic acid via reverse transcription polymerase chain reaction (RT-PCR).
- Due to long turnaround times and complicated logistical operations, a rapid and simple field test alternative is needed to diagnose and screen patients.
- An alternative to the direct detection and measurement of viral load (RT-PCR) is the qualitative detection of specific antibodies to COVID-19. ELISA (discussed in a separate rapid review) and lateral flow immunoassay (LFIA) IgM/IgG rapid test kits are two currently available, qualitative, antibody tests for COVID-19.
- Two low quality clinical trials showed that there is insufficient evidence to support the use of IgM/IgG rapid test kits for the definitive diagnosis of COVID-19. Diagnostic accuracy varies greatly depending on the timing of the test. The test performed very poorly during the early phase of the disease (i.e., less than eight days from onset of symptoms).
- Existing guidelines do not recommend serologic antibody tests for the diagnosis of COVID-19 in currently symptomatic patients.

BACKGROUND

The COVID-19 infections are characterized by highly nonspecific manifestations including respiratory symptoms, fever, cough, difficulty in breathing. These symptoms are also seen as clinical presentations of other virus-related diseases including influenza [1,2].

This poses a challenge in identifying those patients with COVID-19 from individuals with other respiratory diseases. Therefore, there is a need for a diagnostic test that is rapid, accurate and cost efficient that may be used at point-of-care to screen and confirm suspected cases. Early case detection has been proven to have a dramatic effect in controlling infectious disease outbreaks [3].

The current, WHO-recommended gold standard for the diagnosis of COVID-19 is the qualitative detection of SARS-CoV-2 virus nucleic acid via reverse transcription polymerase chain reaction (RT-PCR). RT-PCR is reported to have a sensitivity of 95% and a specificity of 100%; for every 100 COVID-19 positive patients, RT-PCR would have a falsely negative result in 5 patients [4]. The test, however, has limitations such as long turnaround times and complicated logistical operations that makes it infeasible as a rapid and simple field test option to screen and diagnose patients. Another proposed rapid, simple, and highly sensitive way to diagnose COVID-19 is through the qualitative detection of antibodies that are specific to SARS-CoV-2 instead of the direct detection and measurement of viral load through RT-PCR.

Several studies have investigated the use of antibodies in the diagnosis of COVID-19 using ELISA [5,6,7] and lateral flow rapid test kits [8,9]. These studies show different sensitivity and specificity results, and different recommended timing of testing. Disparities between ELISA and lateral flow rapid test results may be due to the longer incubation time for ELISA compared to swift resolution for lateral flow tests, the slow kinetic dissociation rate of ELISA compared to a faster kinetic association rate in lateral flow tests, and the ELISA “capture” antibody and “detector” antibody designations may be reversed in lateral flow tests [10]. Thus, results from studies using ELISA and lateral flow tests should be analyzed separately.

A rapid point-of-care lateral flow immunoassay test product was developed intended for qualitative detection of IgM/IgG in human blood within 15 minutes. It has been designed to be a complementary aid in the diagnosis of patients suspected to have the COVID-19 infection. Limitations of the test include the following: 1) it does not directly confirm virus presence, instead, it provides serological evidence of recent infection, 2) it is not known if the test will cross-react with antibodies to other coronaviruses and flu viruses [8]. Further, studies in patients with Severe Acute Respiratory Syndrome (SARS), a disease also caused by a coronavirus, show that IgM is detectable as early as 3 to 6 days from symptom onset, while IgG is detectable after 8 days, with peak titers at 15 to 20 days [9,11]. This potentially limits the clinical and public health utility of antibody tests for the early diagnosis of coronavirus infections.

Clinical trials that investigate the accuracy and safety of IgM/IgG rapid test kits for diagnosis of COVID-19 patients are still limited.

This rapid review summarizes the available evidence on the accuracy and safety of lateral flow immunoassay (LFIA) IgM/IgG rapid test kits in diagnosing patients with COVID-19. Evidence on the accuracy and safety of the enzyme-linked immunosorbent assay (ELISA) test for COVID-19 are summarized in a separate rapid review.

METHODS

Articles were selected based on the following inclusion criteria:

- **Population:** Symptomatic and asymptomatic COVID-19 patients and suspected COVID-19 patients of any age, with any comorbidities, any severity
- **Intervention:** Antibody/Antigen test, IgM/IgG rapid test kit
- **Comparator:** Reverse Transcriptase Polymerase Chain Reaction (RT-PCR)
- **Outcomes:** Sensitivity, Specificity, Time to detection of antibodies
- **Methods:** randomized controlled trials (RCTs), non-randomized studies, cohort studies, case-control studies, cross-sectional studies

RESULTS

Characteristics of Included Studies

After comprehensive search and appraisal, two (2) completed studies (Appendix 1) and one (1) ongoing trial (Appendix 2) on the accuracy of IgM/IgG antibody test kits for diagnosing COVID-19 were identified.

Li et al., examined 525 blood samples of clinically positive (including PCR test) (n = 397) and clinically negative (n = 128) patients to determine the sensitivity and specificity of the IgM/IgG rapid test kit [8]. On the other hand, Ying et al., investigated 179 patients who were PCR positive (n = 90) and PCR negative (n = 89) comparing the over-all sensitivity and specificity of the antibody test kit and when done between day 0-7, day 8-15, or day 16 and beyond [9]. In both studies, a positive test result was defined as detection of either or both IgM and IgG antibodies to SARS-CoV-2. A negative test result was defined as non-detection of any or both IgM and IgG antibodies to SARS-CoV-2 [8,9].

The ongoing trial (NCT04316728) is designed to evaluate the clinical performance of IgM/IgG antibody test kits in the early diagnosis of COVID-19 in high risk populations. The study will serially test uninfected health-care workers and individuals with chronic conditions (n=200) and is expected to complete data collection by September 2020.

Critical Appraisal

Two studies provided direct evidence on the accuracy of lateral flow immunoassay (LFIA) IgM/IgG rapid test kits in diagnosing COVID-19 compared with PCR and clinical picture as the reference standard. Both studies did not adequately describe the methods used to validate the accuracy of the test kits. As such, it is difficult to ascertain whether or not safeguards to ensure a good estimate of the test kit's diagnostic accuracy were in place; the absence of these safeguards would tend to result in an overestimate of the test kit's diagnostic accuracy. As such, the results of these two studies need to be interpreted with caution.

Accuracy Outcomes

The overall accuracy of the rapid test from the two identified studies are summarized below.

Overall accuracy of IgM/IgG rapid test kits

Author	Sample Size	Sensitivity	Specificity	Positive Likelihood Ratio (LR+)	Negative Likelihood Ratio (LR-)
Li et al	525	88.7%	90.6%	9.46	0.13
Ying et al	179	85.6%	91.0%	9.52	0.16

In majority of cases, Li et al was not able to determine the number of days from symptom onset to the time the blood sample for the rapid test was collected. However, in a subset of patients from one institution (n=58), the blood samples were collected at day 8 to 33 after symptom onset [8].

Ying et al reported the time from onset of illness to blood sample collection in 115 patients. The accuracy of the rapid test kit, stratified according to number of days of onset, is summarized below. The sensitivity (18.8%) of the rapid test was extremely low among those who had their blood samples collected within the first week of symptom onset [9].

Accuracy of IgM/IgG rapid test kits, stratified according to the number of days after onset of symptoms, Ying et al [9]

Day test done	Sample Size	Sensitivity	Specificity	Positive Likelihood Ratio (LR+)	Negative Likelihood Ratio (LR-)
0 to 7 days	25	18.8%	77.8%	0.84	1.05
8 to 15 days	8	100.0%	50.0%	2.0	0.17*
16 days	82	100.0%	64.3%	2.8	0.01*

*During computation, imputation was done for the cells in the 2 x 2 table that had a value zero (0)

Safety Outcomes

No adverse events were reported among the studies reviewed.

Recommendations from Other Guidelines

- The **Chinese Center for Disease Control and Prevention's** Laboratory Testing for COVID-19 Guideline stated that serum antibody tests are utilized as supplementary tests for the following conditions: a) cases that are negative for 2019-nCoV nucleic acid tests and used in addition to nucleic acid tests in diagnosing suspected cases and; b) serological and past exposure surveys of concerned population groups [12].
- The **World Health Organization** recognizes the role of serological assays in research and surveillance but does not recommend it for COVID-19 case detection [13].
- The **European Centre for Disease Prevention and Control** states that SARS-CoV-2 antibody detection tests have limited usefulness in the early diagnosis of COVID-19 because it may take 10 days or more after onset of symptoms for patients to become positive [14].
- **Public Health England**, does not recommend the use of rapid test kits for the diagnosis of COVID-19 infection in community settings [15].
- The **Public Health Laboratory Network** of Australia does not recommend point-of care serology as first line tests in diagnosing acute viral infection due to significant limitations. Validated tests have some utility in determining past infection or screening purposes if used properly by a trained healthcare professional [16].
- The **National Institute of Infectious Diseases** in Japan evaluated anti-SARS-CoV-2 antibodies in blood using an immunochromatography method. They examined 37 cases of

COVID-19 confirmed cases. It was found that virus-specific antibodies in COVID-19 patient sera are difficult to detect up to six days after onset of symptoms [17].

- The **United States Centers for Disease Control and Prevention** recommends the PCR method in diagnosing COVID-19 [18].
- The **Health Technology Assessment Council of the Department of Health** recommended use of IgG and IgM Rapid Diagnostic Test for validation in the local setting and testing should be in parallel with RT-PCR [19].

APPLICATION TO PRACTICE

- In patients with severe acute respiratory infection (ARI), and therefore a high pre-test probability, the rapid antibody IgM/IgG test may be more useful. To illustrate, in a patient with a pre-test probability of 70%, a positive test result (LR +: 9.46) will increase the post-test probability of COVID-19 to 96%. A negative test result (LR -: 0.13) on the other hand, will decrease the post-test probability of COVID-19 to 23%. (Appendix 4, Table 1)

- Conversely, in a patient with mild ARI assuming a pre-test probability of 10%, a positive rapid antibody IgM/IgG test result will lead to a post-test probability of 51% and a negative test result will significantly decrease the post-test probability of COVID-19 to 1.4%. (Appendix 4, Table 1)

- However, on a national policy level, it is important to consider the implications of inadvertently labelling patients as false positives or false negatives. If we use the rapid antibody IgM/IgG test and it truly has the diagnostic accuracy reported in the studies (i.e., 90% sensitivity and 90% specificity), those who will test positive have a 10% chance that they might actually have no COVID-19 infection but will be misdirected to a COVID-19 referral hospital (*false positive*). There, the patient who actually does not have COVID-19 will be exposed to other patients who do have the infection. Conversely, if the rapid antibody test is negative, there is a 10% chance that these patients might actually have COVID-19 and will be misdirected to a non-COVID ward in the hospital (*false negative*). There, the COVID-19-infected patient may potentially spread the infection to non-infected individuals.

- It is also important to note that the diagnostic accuracy of the IgM/IgG rapid test kit is at its best after the first week of symptom onset. This limits the usefulness of the test for identifying infected individuals early, to facilitate timely infection control measures and prevent further transmission of the disease.

RAPID ANTIBODY TESTING AS A SCREENING TOOL

In a hypothetical scenario of 1000 patients with respiratory symptoms and tested for COVID-19 using the IgM/IgG rapid testing kit, we determine the potential outcomes given the following assumptions based on the study of Ying [Ying]:

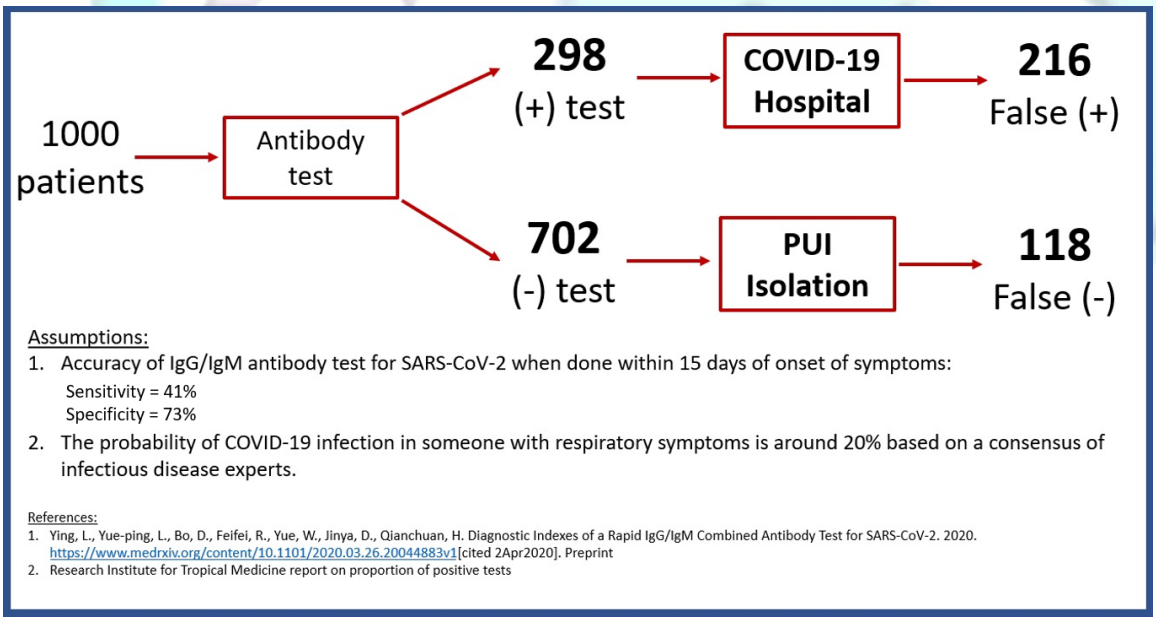
a) Sensitivity of 41% when IgM/IgG rapid testing is done within 15 days from onset of symptoms;
b) Specificity of 73% when IgM/IgG rapid testing is done within 15 days from onset of symptoms;

If the probability of COVID-19 infection in someone with respiratory symptoms is 20% (based on a consensus of infectious disease experts), the outcomes will be as follows, Figure 1:

1) 298 patients will test positive for COVID-19 using the IgM/IgG rapid test and will be admitted to a COVID-19 hospital; but **216 (73%) of these patients are actually false positives and should not be in a COVID hospital.**

2) 702 patients will test negative for COVID-19 using the IgM/IgG rapid test and will be quarantined in community isolation facilities; **but 118 (17%) of these patients are false negatives and should be the ones in a COVID-19 hospital.**

Figure 1: Hypothetical Scenario - Antibody Rapid Testing as a screening tool



CONCLUSION

- Current evidence does NOT support the routine use of IgM/IgG rapid test kits for the definitive diagnosis of COVID-19.
- The diagnostic accuracy of the IgM/IgG rapid test kit varies greatly depending on the timing of the test relative to the number of days from symptom onset. The test performed very poorly (Sn: 18.8%, Sp: 77.8%,) during the early phase of the disease (i.e. less than eight days from onset of symptoms). As such, IgM/IgG rapid test kits are of limited use in the early diagnosis of COVID-19 and is unlikely to be a useful tool to minimize further transmission of the infection.
- None of the reviewed guidelines recommend the routine use of IgM/IgG rapid test kits for the diagnosis of COVID-19.

Declaration of Conflict of Interest

No conflict of interest

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Appendix 1. Characteristics of included studies

Table 1. Characteristics of Included Studies

No.	Title/Author	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Key findings
1	Li et al. 2020 Development and Clinical Application of a Rapid IgM-IgG Combined Antibody Test for SARS-CoV-2 Infection Diagnosis	Cohort study	China	N = 525 397 clinically positive blood samples 128 clinically negative blood samples	IgM/IgG Rapid Test Kits	RT-PCR	Sensitivity: 88.66% Specificity: 90.63% Positive Predictive Value: 96.70% Negative Predictive Value: 72.05% Positive Likelihood Ratio: 9.46 Negative Likelihood Ratio: 0.13
2	Ying et al. 2020 Diagnostic indexes of a Rapid IgG/IgM combined antibody test for SARS-CoV-2	Cohort study	China	N = 179 90 PCR positive 89 PCR negative	IgM/IgG test kit	RT-PCR	Day 0-7 (n=25) Sensitivity: 18.8% Specificity: 77.8% Positive Predictive Value: 60.0% Negative Predictive Value: 35.0% Positive Likelihood Ratio: 0.84 Negative Likelihood Ratio: 1.05 Day 8-15 (n=8) Sensitivity: 100% Specificity: 50.0% Positive Predictive Value: 85.7% Negative Predictive Value: 100% Positive Likelihood Ratio: 2.0 Negative Likelihood Ratio: 0.17 Day 16 or more (n=82) Sensitivity: 100% Specificity: 64.3% Positive Predictive Value: 93.2% Negative Predictive Value: 100% Positive Likelihood Ratio: 2.80 Negative Likelihood Ratio: 0.01

Appendix 2. Characteristics of ongoing clinical trials

Table 2. Characteristics of ongoing clinical trial

No.	Clinical Trial ID / Title	Status	Start and estimated primary completion date	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes

1	NCT04316728 Clinical Performance of the VivaDiag ™ COVID-19 IgM / IgG Rapid Test in Early Detecting the Infection of COVID-19	Not yet recruiting	Start date: March 2020 Est. primary completion date: September 2020	Clinical trial	Italy	n=200 Negative patients defined as adult HCWs with no signs or symptom of coronavirus infection and no known previous history of contact with patients positive for COVID-19, working in a primary care setting; adult patients with at least 2 chronic medical conditions routinely attending a General Practitioner (GP) practice or an outpatients departments or a primary care facility	VivaDiag™ COVID-19 IgM/IgG Rapid Test	PCR	Number of patients with constant negative results Number of patients with positive test with a positive PCR for COVID-19 Overall Number of patients positive for COVID-19 Overall Number of patients negative for COVID-19 Number of patients with contrasting results

Appendix 3. Critical Appraisal of Included Studies

Development and Clinical Application of A Rapid IgM-IgG Combined Antibody Test for SARS-CoV-2 Infection Diagnosis
Li Z, Yi Y, Luo X, Xiong N, Liu Y, Li S, et al.
Journal of Medical Virology. DOI: 10.1002/jmv.25727 Accessed on 30 March 2020

Appraising Directness
Table 4. Comparison Summary of clinical question and research question for appraising directness

	Study Research Question	Rapid Review Clinical Question
P	Patients who conform to the diagnostic criteria of suspected case of COVID-19 according to guideline of diagnosis and treatment of COVID-19 including typical epidemiological history and clinical characteristics	Symptomatic and asymptomatic COVID-19 patients and suspected COVID-19 patients of any age, with any comorbidities, any severity
I	Rapid SARS-CoV-2 IgG-IgM combined antibody test kit	Antibody/Antigen test, IgM/IgG rapid test kit
C	Not specified	Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) and clinical picture
O	Sensitivity, Specificity	Sensitivity, Specificity, Time to detection of antibodies
M	Cohort study	randomized controlled trials (RCTs), non-randomized studies, cohort studies, case-control studies, cross-sectional studies

Appraisal of Validity

Table 5. Criteria for appraisal of validity

Criteria for Appraisal	Rating	Remarks
Was the reference standard an acceptable one?	Yes	(Abstract) “The clinical detection of sensitivity and specificity of this test was measured using blood samples collected from 397 PCR confirmed COVID-19 patients and 128 negative patients….” (page 6) “The respiratory tract specimen, including pharyngeal swab and sputum, was used to confirm COVID-19 cases.”
Was “definition” of the index test and the reference standard independent?	Likely Yes	The criteria of the index test were not defined.
Was “performance” of the index test and the reference standard independent?	Unclear	(page 8) “The tests were done separately at each site.” SARS-CoV-2 IgG-IgM combined antibody tests were done on blood samples of PCR confirmed COVID-19 patients.
Was "interpretation" of the index test and the reference standard independent?	Unclear	However, SARS-CoV-2 IgG-IgM combined antibody tests were done on blood samples of PCR confirmed COVID-19 patients.

Appraising the results
Table 6. Criteria for appraisal of results

What were the likelihood ratios of the various test results?	Sensitivity: 88.66% Specificity: 90.63% Positive Predictive Value: 96.70% Negative Predictive Value: 72.05% Positive Likelihood Ratio: 9.46 Negative Likelihood Ratio: 0.13

Appraising Applicability
The authors mentioned possible cross reactivity with flu and other coronaviruses.

Diagnostic Indexes of a Rapid IgG/IgM Combined Antibody Test for SARS-CoV-2
Ying L., Yue-ping L., Bo D., Feifei R., Yue W., Junya D, Qianchuan H.
Available from: https://www.medrxiv.org/content/10.1101/2020.03.26.20044883v1 Accessed on 2 April 2020 (Pre-print)

Appraising Directness
Table 8. Comparison Summary of rapid review clinical question and study research question for appraising directness

	Study Research Question	Rapid Review Clinical Question
P	inpatient or outpatient COVID-19 cases	Symptomatic and asymptomatic COVID-19 patients and suspected COVID-19 patients of any age, with any comorbidities, any severity
I	SARS-CoV-2 IgG/IgM Antibody Test	Antibody/Antigen test, IgM/IgG rapid test kit
C	SARS-CoV-2 RT-PCR	Reverse Transcriptase Polymerase Chain Reaction (RT-PCR)
O	Sensitivity, Specificity, Accuracy, Positive Predictive Value, Negative Predictive Value, Kappa efficiency with PCR and anti-interference ability	Sensitivity, Specificity, Time to detection of antibodies
M	Retrospective observational study	randomized controlled trials (RCTs), non-randomized studies, cohort studies, case-control studies, cross-sectional studies

Appraisal of Validity
Table 9. Criteria for appraisal of validity

Criteria for Appraisal	Rating	Remarks
Was the reference standard an acceptable one?	Yes	SARS-CoV-2 RT-PCR was used as a reference standard.
Was “definition” of the index test and the reference standard independent?	Likely Yes	The criteria of the reference standard were not defined.
Was “performance” of the index test and the reference standard independent?	Likely No	It was not mentioned if the performance of the index test and reference standard are independent. The study was done retrospectively, and RT-PCR results of included subjects were already known.
Was “interpretation” of the index test and the reference standard independent?	Unclear	It was not mentioned if the interpretation of the index test and reference standard are independent. The study was done retrospectively, and RT-PCR results of included subjects were already known.

Appraising the results

Table 10. Criteria for appraisal of results

What were the likelihood ratios of the various test results?	<u>Day 0-7</u> Sensitivity: 18.8% Specificity: 77.8% Positive Predictive Value: 60.0% Negative Predictive Value: 35.0% Positive Likelihood Ratio: 0.84 (Weakly Positive) Negative Likelihood Ratio: 1.04 (Weakly Negative) <u>Day 8-15</u> Sensitivity: 100% Specificity: 50.0% Positive Predictive Value: 85.7% Negative Predictive Value: 100% Positive Likelihood Ratio: 2.0 (Weakly Positive) Negative Likelihood Ratio: 0 (Strongly Negative) <u>Day 16 or more</u> Sensitivity: 100% Specificity: 64.3% Positive Predictive Value: 93.2% Negative Predictive Value: 100% Positive Likelihood Ratio: 2.80 (Weakly Positive) Negative Likelihood Ratio: 0 (Strongly Negative)

Applicability
Issues that will affect the applicability of IgM/IgG rapid test (in terms of sex, comorbidities, race, age, pathology, or socio-economic) were NOT identified in the course of this appraisal.

Appendix 4. Post-test probability of COVID-19 disease given a test result

Study	Pre-test Probability	Likelihood Ratio		Post-test Probability *Post-test Odds/* *(1 + Post-Test Odds)*
Ying, 2020	20%	Positive (Day 0-15)	1.50	27.3%
		Positive (Day 16 or more)	2.80	41.2%
		Negative (Day 0-15)	0.81	16.8%
		Negative (Day 16 or more)	0	0