Rapid Review Report

Review Title:	**How well does the presence and level of antibodies predict the presence or absence of the disease?**
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Key Findings

- Moderate to strong grade evidence show the overall sensitivity range of IgM, IgG, and combined IgM/IgG are 48.1% to 94.1%, 64.7% to 100%, 83% to 100%, respectively.
- IgM/IgG combined assay, with the posterior probability of 99.15%, has greater accuracy and sensitivity than a single IgM or IgG test.
- The sensitivity of antibody tests is extremely low (~ 11.1%) in the first week following the onset of symptoms but increases rapidly during the second week.
- IgG and IgM titers in patients with severe disease are higher than those in the non-severe patients.
- Antibody tests may detect the presence of COVID-19 in asymptomatic individuals with negative rt-PCR results.

Limitations

- Some of the literature available is in the state of preprint, pending peer review.

GRADE of Evidence: **B - Moderate**

A grade of "B" is assigned when further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate. The review may include one high quality study and/or several studies with some limitations.

Background

SARS-CoV-2 serology assays, such as enzyme-linked immunosorbent assay (ELISA), colloidal gold immunochromatography and direct chemiluminescence immunoassay (CLIA), are developing very rapidly. These have potential advantages, including a fast turn around time, ease of performance, small portable instrumentation, etc. However, whether the antibody presence/levels reflect the presence or absence of the disease needs to be investigated.

Purpose

To assess the specificity and sensitivity of serology (antibody) test.

Research Question(s)

- How well does the presence and level of antibodies predict the presence or absence of the disease?

Method

The rapid review was produced within 48 hours of request.

PICO Statement

P – Patients/Population	Not applicable
I – Intervention/Indication	Not applicable
C – Comparator/Control	Not applicable
O – Outcome	Not applicable

Search Strategy

coronavirus* or corona virus* or coronovirus* or coronaviral or (wuhan adj1 virus) or (wuhan adj1 viral) or cov or covid or WN-CoV or ncov or 2019ncov or ncov2019 or ncovid or ncovid2019 or 2019ncovid or covid-19 or covid19 or covid 19 or corvid 19 or HCov-19 or HCov-2019 or hcov19 or hcov2019 or severe acute respiratory syndrome coronavirus 2 or severe acute respiratory syndrome corona virus 2 or SARS Coronavirus 2 or SARS Corona virus 2 or SARS-COV-2 or SARSCOV2 or SARSCOV 2 or SARS2 or SARS-2 or coronavirus disease 2019 or corona virus disease 2019 or 2019 novel coronavirus infection* or 2019 novel coronavirus disease or 2019-nCoV infection* or coronavirus disease-19 or new coronavirus or novel corona

Inclusion Criteria

Since 2020

Sources

medRxiv Europe PMC Google
Google Scholar National Academies Press
Medline PubMed WHO Global Research on COVID-19
PHAC COVID-19 Up to Date BMJ Best Practice

Summary of Evidence

This is a review of findings from 19 articles, including 10 published/ pending publication papers and 9 pre-prints, which are pending peer review. A summary of the literature is given in Table 1 (attached).

Table 2. Overall accuracy of antibody test

	IgM	IgG	Combined IgM/IgG
Sensitivity	48.1% to 94.1%	64.7% to 100%	83% to 100%
Specificity	81.25% to 96.2%	90.9% to 97.5%	90.63% to 97.5%
Negative Predicative Value	56.72% to 70.2%	90.1% to 90.9%	82.7%
Positive Predicative Value	97.76% to 100%	88.9% to 96.1%	95.1%
Accuracy	77.46%	95.07%	88.3% to 97.3%
Positive likelihood ratios	18.5%	12.65%	
Posterior probability	90.18%	86.26%	**99.15%**

Relationship of antibody tests with patients' clinical condition

Sensitivity of IgM was 79.55%, 82.69%, and 72.97%; IgG was 93.18%, 100%, and 97.30% in moderate, severe, and critical cases, respectively [4]. The accuracy of combined IgG/IgM test was 73.9% in mild/moderate patients and 97.7% in severe/critical patients (with overall accuracy of 88.3%) [6]. IgG and IgM titers in the severe group of patients were higher than those in the non-severe group [7]. Among a group of close contacts who were found to be rt-PCR negative, 4/52 (7.8%) of those with suspect symptoms and 7/148 (4.7%) of those who were asymptomatic were found to be positive for antibodies [7].

Relationship of antibody tests with disease onset

The sensitivity of combined IgG/IgM was 11.1% to 18.8% in patients 0-7 days post disease onset (d.p.o) and went up to 92.9 to 100% in patients 8-15 d.p.o [6, 9]. Fewer than half of patients tested positive on antibody tests during the early phase of illness, i.e. within the first week following disease onset [5,11]. In another report the sensitivity of IgG/IgM in acute phase/ER patients with symptoms was as low as 18.4% [14]. This observed timeframe for the development of COVID-19 antibodies is quite typical for a viral immune response.

Correlation of antibody test with age and gender

One report notes a lower lgM and lgG detection rate in children and youth (less than 18 years old) compared with patients between 18-65 years old and those older than 65 years old [2]. However, another study shows no significant difference in antibody levels in different genders or ages [12].

Cross reactivity

Some test assays are cross reactive with SARS-CoV [8, 16]. It appears that SARS-CoV-2 S1 protein is a specific antigen for COVID-19 diagnosis [5, 8]. Very few test assays are cross reactive with other four endemic human coronaviruses (OC43, NL63, HKU1, 229E), which cause mild clinical symptoms [1, 19].

Types of specimen

Studies show high consistency among samples from fingerstick blood, serum and plasma of venous blood [9, 18].

Conclusions

The overall sensitivity ranges of IgM, IgG, and combined IgM/IgG are 48.1% to 94.1%, 64.7% to 100%, 83% to 100%, respectively. An IgM/IgG combined assay has greater sensitivity than either an IgM or IgG assay alone. The sensitivity of any antibody test is extremely low (as low as 11.1%) during the first week after symptom onset but climbs rapidly from the second week on. IgG and IgM titers in severely affected patients are higher than those with mild to moderate symptoms. Antibody tests may detect the disease in mild or asymptomatic cases who have negative rt-PCR results. SARS-CoV-2 serology tests may cross react with SARS-CoV.

Glossary

Sensitivity: The ability of the test to detect disease when present (positivity in the presence of disease).

Specificity: The ability of the test to detect only the disease sought (negativity in the absence of disease).

Negative Predicative Value: Probability of disease when test is positive.

Positive Predicative Value: Probability of no disease when test is negative.

Prevalence: Proportion of a particular population found to be affected by a medical condition at a specific time. The prevalence of the disease in the population affects predictive value. When disease prevalence is low, the PPV declines, the NPV increases. Sensitivity and specificity are not affected by prevalence.

Accuracy: Ability of a test to distinguish between groups of patients (disease vs. no disease); a combined measure of both sensitivity and specificity.

Positive likelihood ratio (LR+): The probability of a person who has the disease testing positive divided by the probability of a person who does not have the disease testing positive. A likelihood ratio of greater than 1 indicates the test result is associated with the disease. A likelihood ratio less than 1 indicates that the result is associated with absence of the disease. LR+ = sensitivity/ 1-specificity

Posterior Probability: Revised or updated probability of an event occurring after taking into consideration new information.

Table 1: Summary of Literature

Ref	Sample/population	Method	Sensitivity/specificity	Additional findings	Quality of study
1*	29 convalescent sera (collected at discharge)	SARS-CoV-2 proteome microarray (against protein N, S1)	Combined IgM/IgG: 100% (Se)	Cross activity: IgG against ORF9b: 44.8% IgG against NSP5: 3/19 in pts; 1/21 in control	Moderate
2*	29 control, 79 COVID-19 patients	chemiluminescence-immunoassay (against protein N)	IgG: 82.28% (Se), 97.5% (Sp), IgM: 82.28% (Se) 81.25% (Sp),	lower lgM and lgG detection rate in young pt (< 18 Yo) than >18-65 or > 65 yo	Moderate
3*	153 COVID-19 pts	ELISA assay (against N protein)	IgG and/or IgM: 83.0% (Se)	Abs positive rates very low in the first five days after onset of symptoms, rapidly increased as the disease progressed.	Moderate
4*	133 COVID19 pt: 44 moderate; 52 severe; and 37 critical cases	Commercial antibody detection kit	IgM: 79.55%, 82.69%, 72.97% IgG: 93.18%, 100%, 97.30% in moderate, severe, and critical cases, respectively. (Se)		Moderate
5	214 confirmed hospitalized COVID-19 pts	ELISA assay (against rN and rS protein)	IgM (rN) 68.2%; IgM (rS): 77.1. IgG (rN)70.1%; IgG (rS): 74.3%. rS based test has better sensitivity than rN based test	Positive rate of IgM and IgG < 60% during the early stage of the illness 0-10 d.p.o., and obviously increased after 10 d.p.o. positive rate of IgM dropped after 35 d.p.o.	Moderate
6*	179 COVID-19 pts	Commercial antibody detection kit	Combined IgG/IgM: 85.6% (Se), 91% (Sp). 95.1% (PPV), 82.7% (NPV), and 88.3% (accuracy). Accuracy: 73.9% (mild/moderate) and 97.7% (severe/critical)	Se; Sp; accuracy 18.8%, 77.8% and 40% in pts 0-7 d. p.o 100%, 50% and 87.5% in pts 8-15 d.p.o; 100%, 64.3%, and 93.9% in pts >= 16 d.p.o	Moderate
7*	multi-center cross-section study (285 pt) and a single-center follow-up study (63 pt). A cohort of 52 suspects and 64 close contacts	Magnetic Chemiluminescence Enzyme Immunoassay (MCLIA) kit (against N and S protein)	IgG: 100% at 17-19 d.p.o IgM: 94.1% at 20-22 d.p.o (slightly decreased after 3 wk p.o). median day of seroconversion for both lgG and IgM was 13 d.p.o	IgG and IgM titers in severe group were higher than those in the non-severe. 4/52 suspects, 7/148 asymptomatic close contacts with negative RT-PCR are positive for antibodies.	Moderate to strong
8	10 serum samples from Erasmus + 31 serum samples from Berlin (pending publish)	Different commercial kits: IgG and IgA ELISAs	IgG seroconversion can be reliably confirmed in the second week after disease onset. IgA-based ELISA showed higher sensitivity than the	Cross reactivity with SARS-CoV; S1 is a specific antigen for SARS-CoV-2 diagnostics; antibody levels were higher after severe infection than after mild infections;	Low to moderate

			IgG-based ELISA, the IgG ELISA was showed higher specificity than the IgA ELISA.	detecting antibodies against 2 different antigens might be needed to confirm the findings and avoid false-negative results in surveillance studies.	
9	134 samples from 105 patients (pre-proof)	Colloidal gold-based immunochromatographic (ICG) strip	Sensitivity of Combined IgM/IgG: 11.1% in pts 1-7 d.p.o; 92.9% in pts 8-14 d.p.o;96.8% in pts > 15 d.p.o	whole blood samples and plasma showed Cohen's kappa value of 0.93 (high agreement)	Moderate
10*	8274 suspected cases (proportion of confirmed cases from suspected cases is 33.17%, which is the prior probability);	chemiluminescence immunoassay (CLIA) targeting IgG and IgM	IgG: 96.10% (Se), 92.40% (Sp), 90.10% (NPV) and 96.09% (PPV), 95.07% (accuracy). IgM: 70.24% (Se), 96.20% (Sp), 56.72% (NPV) and 97.76% (PPV), 77.46% (accuracy).	The positive likelihood ratios of single IgM and IgG antibody were 18.50 and 12.65 respectively, and the posterior probabilities were 90.18% and 86.26% respectively. The posterior probability of the two antibodies tandem detection is 99.15%, which can give clinicians quantitative confidence in the diagnosis of COVID-19 from suspected cases	Strong
11	Serial plasma samples (n=535) from 173 COVID-19 pts	Commercial ELISA kits (against RBD, S protein)	Seroconversion rate for Ab, IgM and IgG was 93.1%, 82.7% and 64.7%, respectively. The reason for the negative antibody findings in 12 patients might due to the lack of blood samples at the later stage of illness.	antibodies was <40% (<1 wk d.p.o), 100.0% (Ab), 94.3% (IgM) and 79.8% (IgG) since day-15 after onset.	Moderate
12*	412 healthy sera; 69 sera from COVID-19 pts	Elisa detecting total IgG+IgM (against S1 protein)	Combined IgG/IgM: 97.7% (Se);97.5% (sp); overall accuracy is 97.3%.	21 samples collected within one week of onset are positive. NO significant difference in antibody levels observed between different genders or ages	Moderate
13*	4 COVID-19 pts. Control sera.	Elisa detecting antibodies against RBD and S protein	All COVID19 reacted strongly to both RBD and full-length spike protein while reactivity of the other serum samples only yielded background reactivity.	Reactivity of COVID19 sera was stronger against the full-length S protein than against the RBD. Seroconversion started as early as 3 days	Low
14	30 COVID-19 pts; 30 healthy volunteers; 50 acute phase suspects/ER	VivaDiag COVID‐19 IgM/IgG Rapid Test lateral flow	IgM/IgG: 100% specificity Sensitivity: 63.3% +16.7% (weakly+); 1 of 30 (3.3%) was positive for IgM	No cross reactivity Suboptimal sensitivity: possible explanation is the low antibody titers or a delayed humoral	Moderate

	pts	immunoassay (LFIA)	and negative for IgG. ER pts with symptoms: 18.4% (Se); 91.7% (Sp), 26.2% (NPV), 87.5% (PPV)	response	
15	60 convalescent patients (Onset time of 6-7 weeks)		Sensitivity: IgG: 100% IgM: 78.3%;	IgG titer> IgM titer	Moderate
16	208 plasma samples from 82 confirmed and 58 probable cases. 135 plasma samples from patients with acute lower respiratory tract infections and 150 plasma samples obtained from healthy adults.	IgA, IgM and IgG response were examined by using an ELISA based assay on the recombinant viral nucleocapsid protein; western blot	median duration of IgM and IgA antibody detection were 5 days (IQR 3-6), while IgG was detected on 14 days (IQR 10-18) after symptom onset, with a positive rate of 85.4%, 92.7% and 77.9% respectively. In confirmed and probable cases, the positive rates of IgM antibodies were 75.6% and 93.1%, respectively.	No cross-reactivity of SARS-CoV-2 rNP with human plasma positive for IgG antibodies against NL63, 229E, OC43, and HKU1. Strong cross-reactivity was observed between SARS-CoV positive human plasma and SARS-CoV-2 rNP.	Moderate
17	43 COVID-19 pts; 33 control pts	IgM and IgG chemiluminescence immunoassay (CLIA) kits (against N and S protein)	IgM: 48.1% (Se); 88.9% (Sp); 100% (PPV); 70.2% (NPV) IgG: 100% (Se); 90.9% (Sp); 88.9% (PPV) and 90.9% (NPV)	IgM positive rate almost increased first then decreased over time, however, IgG positive rate increased till 100% and was higher than IgM all the time.	Moderate
18	397 samples from COVID-19 pts; 128 samples from control pts	lateral flow immunoassay detecting IgM and IgG antibodies (against S protein)	Combined IgG/IgM: 88.66% (Se); 90.63% (Sp)	Great detection consistency among samples from fingerstick blood, serum and plasma of venous blood. The IgM-IgG combined assay has better utility and sensitivity compared with a single IgM or IgG test.	Moderate
19	9 COVID-19 pts	Recombinant SARS-CoV-2 Spike-based immunofluorescence test (IgM, IgG).	Seroconversion in 50% of patients occurred by day 7, and in all by day 14.	cross-reactivity or cross-stimulation against the four endemic human coronaviruses in several patients (OC43; NL63; HKU1; 229E)	Moderate

*: pre-print articles; N: nucleocapsid protein (protein N); S: spike protein (protein S); d.p.o: date post onset; Se: sensitivity; Sp: specificity

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